parenchyma left, and one need not worry about hemostasis. The blood supply is much less than normal, the situation is less formidable, and the control of the blood supply is easy.

The other problems are very diverse and very complicated. I am rather surprised that Dr. Davis has not found abscesses' working downward. In our series there were perirenal abscesses gravitating as far as Poupart's ligament. The whole flank was transformed into an infected space. There is no doubt that conservative treatment is the proper kind so long as it is really conservative. In some cases if the patient seems not to be doing well a nephrectomy should be performed.

The problem of the bilateral case is a very difficult one. In my group of 150 cases, 80 or more were associated with stones in one way or another. They either formed the inciting cause of the pylonephrosis or were incidental to it.

Dr. E. Granville Crabtree: In the handling of this group of cases Dr. Davis has brought out many important points. I wish to emphasize the necessity for prompt secondary operation in case it has to be done. In approximately a month's time the patient has had the advantage of adequate drainage of the suppurating process, even in cases where the process is in the parenchyma of the kidney itself. At the end of this time, one does not find the dense scar tissue which makes secondary operations almost impossible. I note in one of Dr. Davis's cases the great difficulty in handling scar tissue. I make an effort to reoperate within a month, because later than that the scar tissue becomes very difficult to deal with.

Dr. Clyde L. Deming: Dr. Davis has clearly outlined the way to handle kidney infections in a conservative manner by two-stage nephrectomies, first draining the ureters and leaving the kidney in. I have recently looked over our list of nephrectomies for pyonephrosis. There are 35 or more, and there has been only 1 death. This is a better record than I find in the literature. There are large numbers of cases where kidneys have been preserved, and 1 case that I should like to cite. A woman with bilateral pyonephrosis had only 10 per cent dye excreted in two hours. She was operated on nine years ago by conservative measures and the pus was drained by nephrostomy and later by dilatation of the ureters. The renal function has remained about the same; the patient does her own housework and looks quite well. In cases with pyonephrosis there have been no deaths from nephrectomy during the last few years; we have tried to treat these cases conservatively by two-stage operations.

I have lost cases by doing a primary nephrectomy and have wondered why there was shock. This occurs within two to twenty-four hours after operation, and there seems to be no way of combating it. Recently there have been reported a number of cases in which the patients died of shock and in which autopsy showed a single adrenal. That brings to my mind a new possibility, which I think has not been brought out, namely in some cases where we attempt nephrectomy there is only one adrenal. We all know that we sometimes injure the adrenal in doing a nephrectomy, and it is possible that these deaths may be explained by injury to this single gland.

In doing two-stage nephrectomies one finds a rather marked diminution in the size of the kidney, so that the operation is very much easier, the line of cleavage is more distinct from the adrenal, and one is less likely to injure the gland in removing the kidney.

Dr. Davis did not bring in the factor of different types of infection in discussing the treatment. I wonder if he has formulated any opinion as to the types of infection in which special kinds of surgical treatment should be applied.

Dr. J. Dellinger Barney: Dr. Davis has reviewed the subject most thoroughly. I think one should lay down the rule that each case is a law unto itself. It is surprising that one can leave behind a great amount of inflammatory tissue in the form of perirenal fat and capsule in cases of intracapsular nephrectomy. It is unwise to remove it, and to do so takes as much time as does a whole nephrectomy. I can think of only one or two cases where I have later removed this tissue. Nature seems to have been kind in these cases, and it is poor judgment to take out the tissue when it can be left behind. Some of the older men used to tell me to remove everything possible, but I have found this inadvisable.

Dr. Davis (closing): Dr. Quinby has raised a point which I did not mention, that there are a few cases which do not do well after nephrostomy drainage. That is true, and I think it is due to the conformation of the kidney pelvis itself. It may be difficult to obtain good drainage by a single drainage tube or even two. I recall one case where it was obvious that nephrostomy drainage would be unsatisfactory, and I proceeded to perform a primary nephrectomy. The patient was extremely ill and I feared she would die of operative shock, but fortunately she made an excellent and rapid recovery. I think this was one case which would not have done well with nephrostomy drainage.

Dr. Crabtree speaks of the time of secondary operation. I agree with him. The patient who was operated on six months later went too long, owing to her failure to return at the recommended time. On the other hand, in a good many cases the patient is so debilitated because of the first illness that one feels it desirable to postpone secondary operation until the patient's condition has improved. Patients are often quite emaciated and anemic, and it takes two or three months to build them up sufficiently to withstand the operation.

As Dr. Deming has said, one often finds the adrenal extending onto the kidney. In some cases where we have done extracapsular nephrectomy, an intracapsular operation would have been better.

As to the types of infection, those due to Proteus bacilli seem to be the most difficult ones to treat. If one can get thorough drainage with two or three drainage tubes, and possibly a Dakin's tube as well, and irrigate the kidney with acetic or phosphoric acid in dilute solution, he can deal successfully with a Proteus infection.

I was delighted to have Dr. Barney confirm my impression that it is correct to leave large amounts of fibrous tissue behind. If it is necessary to drain, the most important point is keeping the drainage material in place for a long time until the wound can heal from the bottom with granulation tissue. I think it is the early removal of drainage tubes that gives trouble in these cases.

INTRAPERITONEAL RUPTURE OF THE URINARY BLADDER

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WITH the present-day incidence of automobile and industrial accidents the therapeutic problems incident to trauma to the urinary bladder are becoming increasingly impressed upon the conscience of the profession. Of all the conditions resulting from trauma to the genitourinary organs, intraperitoneal rupture of the bladder is one of the least common, a fact which is adequately explained by the protection afforded by the bony pelvis. Nonetheless, it occurs with sufficient frequency so that all should be familiar with its clinical picture and the therapeutic problems involved, for it presents an emergency that demands immediate surgery if the patient is to survive.

In an effort to evaluate and co-ordinate some of the numerous published opinions as to diagnosis and treatment of this condition, a study was conducted of 22 cases proved at operation or autopsy at the Boston City Hospital during the past twenty years. During the same period 19 cases of extraperitoneal rupture of the bladder have been operated upon. In addition there have been a great many cases of suspected intraperitoneal or extraperitoneal rupture in which, for one reason or another, the exact diagnoses have not been definitely established. These cases have been excluded, with the result that the series is smaller than is desirable for statistical analysis, yet has the great advantage that there can be no doubt as to the exact diagnosis in each individual case.

HISTORICAL

Homer[19, 20] is credited with having mentioned wounds of the bladder causing death, while Hippocrates stated that such wounds were invariably fatal. For many centuries there was little reason to doubt the accuracy of the latter observation, for in 1882 Rivington[32] stated that he doubted whether there had ever been an unequivocal recovery following intraperitoneal rupture. He added that "I do not, in this age of antisepsis, absolutely despair of a time arriving when such can no longer be said." Bell, in 1789, is credited with first having proposed suture of the ruptured bladder, while Grandchamps,[17] in 1826 concluded from animal experiments that the bladder wall could be closed by suture of the muscular and serous coats. By 1888, Grant[18] was able to collect 14 cases of intraperitoneal rupture from the literature, all treated by operation. Of these 14 cases there were 5 recoveries and 9 deaths. Since that time there has been an increasing number of case reports, but with few efforts at critical evaluation of the several methods of surgical therapy.

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AGE AND SEX INCIDENCE

Intraperitoneal rupture of the urinary bladder can occur in either sex and at any age. Evidence for this statement is found in the present series, which includes a girl of three and a man of seventy-four. As would be expected, however, men between twenty and forty are most frequently afflicted, since they are more exposed to the dangers of trauma and alcoholism. In the series herewith presented there were 16 men and 6 women, a ratio of 3:1. The average age was forty-one years, the male patients averaging forty-five, and the female thirty-two.

ETIOLOGY

Trauma is by far the most frequently encountered etiologic agent in intraperitoneal rupture. The traumatizing force is usually applied directly to the abdominal wall in a person who at the moment has a distended bladder. Since it takes at least 350 cc. of fluid to bring the dome of the bladder above the brim of the pelvis, and since this amount of urine is not comfortably tolerated by the normal adult, it is not surprising to find that alcoholism, which not only dulls the sensorium but also causes an increase in urinary output, is very frequently encountered. Of the 22 cases in this series 12 (55 per cent) gave a history of direct trauma to the abdomen (usually a kick in the abdomen, a fall on the abdomen or being crushed between moving objects). Of the 12 cases in which trauma was a major etiologic agent, 5 were in addition alcoholic at the time of rupture. In 2 cases of alcoholism associated with intraperitoneal rupture, no history of trauma could be obtained. This supposed absence of trauma, of course, is open to question. However, in one of these cases the patient was awakened from a drunken stupor by the sudden onset of agonizing abdominal pain, the cause for which was later found to be an intraperitoneal rupture of the bladder.

Intraperitoneal rupture is an occasional complication of the second stage of labor, as was the case

with 1 patient in this series, in whom a difficult forceps delivery was complicated by partial inversion of the fundus of the uterus. About forty-eight hours after delivery a tumor mass was palpated in the pelvis which at operation proved to be a walled-off abscess in contact with a small rent in the posterior wall of the bladder.

Disease of the bladder wall is an occasional factor in the causation of rupture. Alton[2] has reported a case of intraperitoneal rupture wherein at autopsy the entire wall of the bladder was found to be necrotic, owing to tuberculous infection which evidently originated in the left kidney. Dixon and Strohl[13] report an unusual case of spontaneous rupture of the bladder in a patient with syphilis of the central nervous system.

Saphir and Shapiro[33] reported a case of seemingly spontaneous intraperitoneal rupture in which microscopic examination of the bladder wall showed almost complete replacement of the muscularis with fat. Careful microscopic examination of bladder walls of patients coming to autopsy from diseases not related to the urinary tract showed 2 cases of fatty infiltration in 30 bladders examined; bladder function during life had apparently been normal. These cases suggest fatty infiltration of the bladder wall as an occasional etiologic factor in the production of so-called spontaneous rupture. No such findings were recorded in the present series.

The term "spontaneous rupture" is reserved for cases in which there is no history of trauma and no demonstrable disease of the wall of the bladder. Three such cases were found in this series, of which 1 had a postprostatectomy stricture of the urethra. Genitourinary disease was not demonstrable in the other 2 cases. Of these, 1 was of particular interest in that the patient, a man of forty-eight, was awakened from a sound sleep by sudden, severe abdominal pain which he tolerated for forty-eight hours before entering the hospital. At laparotomy, an 8-cm. laceration was found in the dome of the bladder. This was closed after the method to be described shortly and the bladder was drained by means of a urethral catheter. The patient made an uneventful recovery, and when last seen six months after operation he was voiding normally and without residual urine. Cystoscopy at this time showed a perfectly normal bladder mucosa except for the barely perceptible scar at the site of closure.

Two cases of this series showed definite disease of the bladder. In one the bladder wall was infected to the extent that it was described as being phlegmonous. In the other rupture occurred through a diverticulum of the bladder wall.

Table 1. *Etiology of 22 Cases of Intraperitoneal Rupture of the Urinary Bladder.*

	NO. OF CASES	ALCOHOLIC
Direct trauma to abdomen	12	5
Trauma (type unknown)	2	1
Spontaneous	3	1
Bladder irrigation	1	
Transurethral resection of prostate	1	
Birth trauma	1	
Disease of bladder wall:		
diverticulum	1	
phlegmon	1	
Totals	22	7

Table 1 summarizes the etiologic factors responsible for rupture of the bladder in the 22 cases in this series.

PATHOLOGY

In the majority of cases the actual dissolution of continuity of the bladder wall is represented by a linear tear which, even with the bladder in the contracted state, is usually 5 cm. or more in length. The laceration, in the majority of cases, runs from a point on one side or the other of the posterior wall, obliquely across the dome to the anterior portion of the opposite side. Because of this anteroposterior direction, it is often difficult to effect adequate surgical closure of the posterior extremity of the laceration.

In an effort to determine the mechanism of rupture of the bladder, Besley[5] injected fluid into the bladders of 6 cadavers, to the point where the bladder wall ruptured. From these experiments he concluded as follows: (1) There is no constant relative order of tearing of the coats of the bladder. (2) When pressure is applied evenly throughout the bladder the wall ruptures at the weakest point, which is not always the same, anatomically speaking; thus, in 5 of the experiments an intraperitoneal rupture was produced, while an extraperitoneal rupture occurred in the sixth case. (3) In no case did the bladder rest against the promontory of the sacrum, so that this bony projection has nothing to do with the mechanism of rupture.

The sudden expulsion of the contents of the bladder into the peritoneal cavity represents a shock which is tolerated surprisingly well. It is not unusual to find cases reported in which recovery has ensued when surgery has not been resorted to until forty-eight to sixty hours after rupture. Indeed, Quick[31] reported recovery in a case operated upon ten days and fourteen hours after rupture.

The urine itself is irritating to the peritoneum, and sets up a chemical peritonitis which is similar to that following perforation of a peptic ulcer. If the urine is bacteriologically sterile, this chemical insult is well tolerated. However, if the urine is

infected, as is frequently the case in the presence of chronic bladder-neck obstruction from any cause, the immediate chemical insult to the peritoneum sets the stage for the subsequent growth of bacteria from the infected urine. A septic peritonitis which carries a high mortality results. Because low-grade urinary infection is frequently present in persons in the older age groups, it is evident that early operation affords the best protection against the dissemination and growth of bacteria in the peritoneal cavity.

As bladder rupture is most frequently the result of trauma, it is to be expected that in many cases associated injuries will be present to complicate the clinical picture. Of the 14 cases in this series in which rupture was due to trauma, 8 showed no other demonstrable injury of clinical significance. Four patients suffered from fracture of the pelvis, of which 1 had in addition a rupture of the sigmoid flexure of the colon. A fifth had a fracture of the os calcis, and a sixth had a compression fracture of the cervical spine.

Campbell[9] reports that of 166 cases of fracture of the pelvis seen at the Bellevue Hospital, 15 per cent had also a rupture of the urinary bladder, either intraperitoneal or extraperitoneal. On the other hand, 20 per cent of 55 cases of rupture of the bladder, both intraperitoneal and extraperitoneal, had in addition a fracture of the pelvis.

As mentioned under the discussion of etiology, associated genitourinary disease is occasionally present, and more rarely is responsible for the rupture. In this series is reported 1 case of cystitis and diverticulitis, 1 case diagnosed clinically as phlegmon of the bladder, and 2 cases of bladder-neck obstruction, 1 a postprostatectomy stricture and the other a benign hyperplasia of the prostate.

CLINICAL PICTURE AND DIAGNOSIS

The clinical picture of intraperitoneal rupture of the urinary bladder is frequently misleading. The usual picture is one of an acute abdominal catastrophe following immediately, or soon after, a definite trauma to the abdomen. The patient complains of abdominal pain and, very often, marked frequency and urgency of urination, occasionally of anuria. Examination reveals signs of a rapidly progressive peritonitis, with board-like rigidity of the abdominal muscles and generalized tenderness and rebound tenderness. A boggy induration in the posterior cul-de-sac can occasionally be made out on rectal or vaginal examination. The majority of cases give a history of gross hematuria which, in conjunction with the complaint of frequency and strangury, usually points to the genitourinary apparatus as the site of injury. In 21 cases of this series a definite statement concerning the presence or absence of hematuria was noted. Of these, hematuria was present in 13 (62 per cent).

In cases where rupture occurs without trauma, of which there were 5 in this series (including 2 due to disease of the bladder wall), the clinical picture is much the same, although because of its rarity the diagnosis is frequently obscured since the physician does not consider the urinary bladder in association with the sudden onset of peritonitis. In these 5 cases, 3 patients were awakened by the sudden onset of abdominal pain. In the fourth case, rupture occurred while the patient was under observation in the hospital preparatory to an operation for hydrocele. In the fifth the patient was very sick with pneumonia and died without recognizable abdominal symptoms, and intraperitoneal bladder rupture was not suspected until found at autopsy.

Since a history of trauma may or may not be present, the condition must be differentiated from other and commoner causes of generalized peritonitis of acute onset. These include perforation of a peptic ulcer, acute fulminating appendicitis, ruptured ectopic pregnancy, and so forth. In addition, because of the frequency of alcoholism in these patients, acute alcoholic gastritis with its frequently confusing clinical picture must be ruled out.

To aid in the differential diagnosis, in addition to the very important finding of blood in the urine, we have several clinical tests which may at times prove of great diagnostic importance. The first of these is the well-known, but often misleading, injection test, which consists of injecting through a catheter a known amount of sterile fluid into the previously emptied bladder and noting the amount expelled. If the quantity returned is appreciably less than the quantity injected, this fact supports the diagnosis of intraperitoneal rupture. However, the result of this test depends to a great extent on the type and degree of laceration, and a negative result (that is, fluid expelled equals fluid injected) is without significance. This is readily explained, since if the laceration is small only a minor amount of fluid will escape into the peritoneal cavity, and the quantity returned will so nearly equal the quantity injected that the difference will not be readily measurable. On the other hand, if the laceration is large and open, allowing a free interchange of fluid between bladder and peritoneal cavity, the injected fluid entering by way of the bladder will be returned by the same route and again the quantities of injected and returned fluid will be approximately equal. Thus, the only case in which the injection test will be positive is that where fluid injected into the bladder has free access into the peritoneal cavity but, be-

cause of a valve-like action, the return flow is impeded. The injection test gave positive information in only 4 cases of this series.

The results of simple catheterization may at times give information which is very misleading, as evidenced by Case 22 of this series. The patient was admitted with a history of symptoms of peritonitis with a total anuria of thirty-six hours' duration. On admission, a catheter was passed into the bladder, yielding 60 cc. of clear, yellow urine. An hour later a catheter was again passed and yielded 2000 cc. of grossly bloody urine. At operation an 8-cm. laceration was found extending across the dome of the bladder in an anteroposterior direction. It is evident that at the first catheterization the catheter was introduced into the bladder, which contained a small amount of grossly normal urine. At the second catheterization it was introduced through the rent into the peritoneal cavity, yielding a large quantity of bloody urine which had been intermittently escaping from the bladder since the rupture had occurred.

Keen[24] in 1890 suggested the injection of filtered air into the bladder as an aid in diagnosing intraperitoneal rupture. He pointed out that if rupture were present the injected air would escape into the peritoneal cavity and distend the entire abdomen, whereas if it were not present the resulting area of tympany would be confined to the hypogastric area. Walsham is credited by Besley[5] as being the first to apply this test clinically, in 1895. Alexander,[1] in 1901, warned against the massive injection of air, stating that if an intraperitoneal rupture were present the inflation of the peritoneal cavity might lead to a fatal syncope. More recently, Vaughan and Rudnick[39] have suggested the injection of a small quantity of air (50 to 100 cc.). If intraperitoneal rupture is present a roentgenogram of the abdomen taken with the patient in the upright position will reveal air between the liver and diaphragm, while if an extraperitoneal rupture is present the air will escape into the fascial planes of the abdomen and thighs, where it will be readily visible in the x-ray picture. We have had no experience with either of the air injection tests, but the feasibility of Vaughan and Rudnick's suggestion can hardly be doubted.

Cystoscopy cannot be recommended as a diagnostic aid in the presence of intraperitoneal rupture of the bladder, since at best it is time-consuming and an ordeal for a patient who is already seriously ill. In the occasional case in which the diagnosis is obscure and the rent in the bladder is small or incomplete, cystoscopy may prove to be of value.

TREATMENT AND MORTALITY

As in the case of rupture of any abdominal viscus, the treatment of intraperitoneal rupture of the urinary bladder is purely surgical. In this series there are 3 cases in which no treatment was instituted and which ended fatally. In each case the clinical diagnosis was missed and the condition was discovered only at autopsy. It is probably correct to state that untreated intraperitoneal rupture of the urinary bladder is invariably fatal.

In reviewing the literature relative to intraperitoneal rupture of the bladder, one is astounded at the lack of agreement among authors as to what actually constitutes adequate surgical treatment. For treatment of the actual laceration, most authors have recommended a double row of inverting sutures of catgut. Crosbie[12] and Dixon and Strohl[13] have, on the other hand, recommended adequate suprapubic drainage of the bladder with no attempt to suture the laceration. Each author reports successfully treated cases. As to whether or not to drain the peritoneal cavity, opinion is similarly divided. In the majority of cases reported a drain has been placed in the posterior cul-de-sac. Cave[11] states, however, that "unless there is present a localized peritonitis with abscess formation, drains placed into the peritoneal cavity are of questionable value." O'Neil[30] advocates sewing the cavity up tightly without drainage. Smith[36] has recently reported a case in which, after careful suture of the bladder, the peritoneum was closed without drainage with good result. Nicolaysen[29] reports 1 case treated successfully by urethral catheter drainage alone.

The question of how best to drain urine from the bladder postoperatively is also a mooted one. MacCormac[26] reported recovery in 2 cases in which no provision was made for the escape of urine other than by encouraging the patients to void at frequent intervals. Grant[18] recommended emptying by means of repeated urethral catheterizations. He believed that even this precaution might be omitted after four days. Campbell[9] and others[16, 38] have stressed the importance of liberal suprapubic drainage. However, many successful cases have been reported in which urethral catheter drainage has proved to be entirely adequate.

In an effort to evaluate the relative accuracy of these conflicting opinions, the present series was subdivided according to whether the bladder wall was sutured, whether bladder drainage was instituted, and if so the type of drainage, and finally whether the peritoneal cavity was drained. Vari-

ous combinations of these variables are presented in Table 2. The various groups are too small for statistical comparison, yet give a general conception of the types of treatment adopted together with the results obtained.

Table 2. *Summary of Methods of Surgical Treatment.*

BLADDER SUTURE	BLADDER DRAINAGE	PERITONEAL DRAINAGE	RECOVERED	DIED	MORTALITY %
Sutured	Suprapubic	Drained	2	1	33.3
Sutured	None	None	1	0	— —
Sutured	None	Drained	5	2	28.0
Sutured	Urethral	None	1	1	50.0
Not sutured	Urethral	Drained	1	2	66.6
Sutured	Suprapubic	None	0	1	100.0
Sutured around suprapubic drain	Suprapubic and Urethral	Drained	0	1	100.0
Not sutured	None	Drained	0	1	100.0
No treatment			0	3	100.0
Totals			10	12	55.0

In Table 3, a condensation of Table 2, an effort has been made to determine the importance of the several single factors in surgical treatment. From it we may conclude that the single factor of peritoneal drainage is not of statistical importance in this series if the other factors of treatment are disregarded. Ignoring all points in treatment except that of drainage of the bladder, we find that in cases in which urethral catheter drainage was used a mortality of 36 per cent ensued. Suprapubic drainage, on the other hand, carried a mortality of 50 per cent, while 2 of 3 cases in which no provision for drainage of the bladder was made died, a mortality of 67 per cent.

Table 3. *Evaluation of Methods of Treatment.*

	TOTAL CASES	DIED	MORTALITY %
Peritoneal cavity drained	15	7	47
Peritoneal cavity not drained	4	2	50
Suprapubic drainage	4	2	50
Urethral catheter drainage	11	4	36
Both suprapubic and urethral catheter drainage	1	1	100
No bladder drainage	3	2	67
Suprapubic drainage plus peritoneal drainage, with or without suture of bladder	3	1	33
Urethral catheter drainage plus peritoneal drainage, with or without suture of bladder	9	3	33

Disregarding for the moment the method of dealing with the lacerated bladder wall, we find in cases in which peritoneal drainage was established that suprapubic and urethral catheter drainage carried the same mortality — 33 per cent. However, when the lacerated bladder wall was sutured *and* the peritoneal cavity drained, suprapubic bladder drainage carried no mortality in 2 cases. Under the same circumstances, urethral catheter drainage carried a mortality of 28 per cent in 7 cases (Table 2).

From these considerations it is evident that the treatment of a given case must be governed by the patient's general condition and the findings at operation. In the first place, the type of bladder drainage used is not important statistically provided it is adequate. This means that it must prevent a head of pressure from forming against the suture line. If it is technically possible to effect a sound closure of the laceration by means of a double layer of inverting sutures in a young individual who gives no history of previous bladder-neck obstruction, then urethral catheter drainage is adequate and has the advantage of a quicker postoperative convalescence, since there will be no delay caused by a slowly closing suprapubic sinus. On the other hand, if any doubt exists as to the efficacy of the suture line, suprapubic drainage is undoubtedly safer and the speed of convalescence is of secondary importance.

Similarly, in the young individual subjected to traumatic rupture of the bladder in whom there is no reason to suspect pre-existing urinary infection, and who is operated upon within a reasonable time after the rupture has occurred, it is probably safe to close the peritoneum without drainage. But in the older patient in whom there is a possibility of urinary infection, or in any patient, young or old, in whom operation is for any reason delayed beyond ten hours, drainage of the posterior cul-de-sac should be instituted in an effort to prevent an infectious peritonitis.

As has been stated above, it has been held that after suprapubic drainage of the bladder suturing of the bladder wall is unnecessary. In this series, 1 patient so treated died, as did another when the tube was sutured into the laceration itself. In this respect we are inclined to agree with Cave,[11] who states that "the patient's condition warranting, the expenditure of ten minutes' additional time for repair by suture seems more than worth while."

A further factor of greatest importance in influencing the mortality of intraperitoneal rupture is the time elapsing from injury until surgical treatment is instituted. In Table 4 the 19 surgically treated cases in this series have been divided into groups according to the time between rupture and surgical treatment. While the number in each group is small, the tendency for the mortality to increase directly with the time between injury and operation is probably accurate, and speaks for operation at the earliest possible moment.

The mortality for the series of treated cases was 47.4 per cent, which compares favorably with that reported from other clinics.[5, 9, 23, 28, 37, 38]

SUMMARY AND CONCLUSIONS

Trauma not infrequently associated with alcoholism is the commonest etiologic agent encountered in intraperitoneal rupture of the bladder.

The laceration of the bladder wall usually runs in an anteroposterior direction across the dome of the bladder. Because of the obstacles to exposure, adequate closure of the posterior extremity of the laceration is often difficult.

A discussion of the special tests whereby the diagnosis of intraperitoneal rupture of the bladder may be definitely established is presented. Although we have had no experience with the suggestion of Vaughan and Rudnick that air be injected into the bladder, the method seems logical and worthy of trial. In the event of intraperitoneal rupture a roentgenogram of the abdomen taken in the upright position will disclose air in the subdiaphragmatic space.

Table 4. *Mortality According to Time between Rupture and Operation.*

ESTIMATED TIME	NO. OF CASES	RECOVERED	DIED	MORTALITY
				%
Less than 12 hours	6	4	2	33
12-24 hours	7	4	3	43
24-48 hours	2	1	1	50
48-72 hours	0			
Over 72 hours	4	1	3	75
Totals	19	10	9	47

Treatment of intraperitoneal rupture of the bladder is purely surgical and should encompass three aims, namely the treatment of the laceration of the bladder wall, the treatment of the peritoneum, and the method of establishing adequate drainage of bladder urine. A discussion of these factors and their relative importance is presented.

The mortality is directly proportional to the time elapsing between rupture and the institution of adequate surgical treatment.

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RECENT PROGRESS IN PHYSIOLOGY

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"WE seek truth itself," wrote Claude Bernard[1] in *La Science Expérimentale*, "and if we continue ever to seek it, it is because the part of it that we have already found does not satisfy us." Priestley[2] also recognized that the scientist's search for truth yielded only fragments, some of them important, and all making up the general body of fact constituting a science when he wrote:

> In completing one discovery we never fail to get an imperfect knowledge of others, of which we could have no idea before; so that we cannot solve one doubt without creating several new ones.
>
> Travelling on this ground resembles Pope's description of travelling among the Alps, with this difference, that here there is not only a *succession*, but an *increase* of new objects and new difficulties.
>
> "So pleas'd at first the tow'ring Alps we try,
> Mount o'er the vales, and seem to tread the sky.
> Th' eternal snows appear already past,
> And the first clouds and mountains seem the last.
> But those attained, we tremble to survey
> The growing labours of the lengthen'd way.
> Th' increasing prospect tires our wand'ring eyes,
> Hills peep o'er hills, and Alps on Alps arise."

Difficulties of perspective must always concern him who attempts to write on progress in physiology rather than to present a review of the recent literature. Discoveries which seem of the greatest importance when first announced may later be found to be mere foothills hiding from sight a great peak. So also a great discovery, seen unclearly, may appear as an insignificant landmark until great effort and years of progress reveal it in its true stature. The history of physiology is replete with examples of this kind. The discovery of ganglia in the heart by Remak,[3] once hailed as the final proof of the neurogenic theory of the heart beat, is the classic example of the first type, while Purkinje's discovery[4] of the peculiar fibers along the inner walls of the chambers of the heart shows what great importance may some day be attributed to a long-neglected observation.

If one can at all distinguish the contributions in physiology in the past years, it is in the brilliant application of Claude Bernard's insistence on the essential unity of phenomena in living and nonliving systems, and the necessity of studying them by the same methods. It will be recognized from what follows how greatly the physiologist is indebted to the chemist, and especially the physicist, who thus repays the physiologist for teaching him how to make electricity by the union of two dissimilar metals.

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THE PHYSIOLOGY OF NERVE AND MUSCLE

Muscular Contractions

Few aspects of physiology have been studied as long or as fruitlessly as that which relates to the intimate nature of muscular contraction. The last few years, however, have seen the development of a method that holds great promise for the future of this subject, namely the method of x-ray diffraction so ably employed by Astbury and his co-workers.[5–12] Their work is based primarily on earlier demonstrations by the same technic as that which shows that silk fibers are made up of bundles of protein molecules composed of alternate molecules of alanine and glycine in the classic polypeptide linkage of Fischer. From a stereochemical viewpoint, these molecules were shown to be fully extended, and thus incapable of elongation and elastic recoil. The molecules composing hair or other keratin structures, which are known to be elastic over a wide range, were then demonstrated to exist normally in a state of partial contraction owing to the formation of temporary ring structures, probably as a result of attraction between the side chains. When stretched to the limit, these molecules assume a fully extended structure in every way similar to the natural state of silk molecules. Next, it was shown that under the influence of initial stretch plus steam, the normally partially contracted molecules of hair would pass into a still shorter or supercontracted state, again by the formation of further ring structures.

These observations upon keratin were then extended to dried films of the muscle protein myosin, which showed an identical behavior. Such films normally exist in the partially contracted or α keratin state, and can be stretched out to the fully extended or β keratin state. Under the influence of steam and initial tension they also pass into a state of supercontraction. Washed and dried muscle of the foot retractor of *Mytilus edulis* has also been demonstrated to be composed of similar longitudinal bundles of polypeptide chains existing in the partially buckled or α keratin state, and capable of being stretched to the fully extended state.

The implication is clear that the contraction of muscle may be due to the actual shortening of the molecules of protein which make up the greater proportion of its substance, corresponding to the supercontraction of protein chains in hair and myosin films. That this is actually the case has not of course been demonstrated as yet, but such an explanation would fit in with many of the known facts of muscle physiology. It would, for instance, explain the well-known effect of increased initial tension in promoting vigorous contraction, which finds such striking application in Starling's law of the heart. Bernal[13] has recently shown how the cross-striations seen in many types of muscle may be accounted for by the twisting of such long molecules along the longitudinal axis of the muscle fiber, an idea also suggested by Tiegs,[14] and it is not improbable that the change in the cross-striations during muscular contraction is due to a different degree of twisting, associated with a more acutely buckled molecule. The work of Bernal also indicates how ionic changes produced by electrical stimulation or by the action of large positively charged ions such as potassium may bring about shortening of unstable molecules, while such ions as calcium may exercise a stabilizing influence.

The Compound Nature of the Action Potential and the Reaction to Subthreshold Stimulation

The classical researches of Erlanger and Gasser have led to so many basic advances in physiological thinking that to attempt any sort of comparative evaluation is futile. There are two recent developments,[15, 16] however, which seem to hold infinite promise. The first of these is the elucidation of the compound nature of the monophasic action potential and the association of coincident changes in threshold with its various parts. It is now recognized that the single monophasic action potential is made up of at least four parts: (1) the spike, a brief period of negativity associated with the local discharge of the propagated disturbance; followed by (2) a brief positive afterpotential not always found; (3) a somewhat longer negative afterpotential; and (4) a much longer positive afterpotential. A great many procedures have been employed to demonstrate that these four parts are actually separate processes capable of independent variations.

These portions of the electrical disturbance following discharge of the impulse in an excitable tissue have next been correlated with changes in threshold. It is known that the duration of the spike coincides with the absolutely refractory period, the first positive afterpotential with the relative refractory period, the negative afterpotential with the supernormal period, and the second positive afterpotential with a prolonged period of relative inexcitability. Thus the classic picture of the threshold changes following a propagated disturbance is enlarged to include a final, fairly prolonged period of heightened threshold of which physiologists had been unaware, and the relation of these changes to alterations in potential is demonstrated.

The applications of these discoveries to many fields have already been numerous, but an especially significant one to simple nerve fibers deserves attention. This is the implication of the second positive afterpotential and the negative afterpotential in the production of rhythmic discharge. In conditions in which the supernormal period is not in great evidence, relatively slow rhythms comparable to that of the heart are set up by the application of constant stimuli, in which the limiting factor seems to be the positive afterpotential. Under circumstances in which the supernormal phase is pronounced, more rapid rhythms or tetany are produced in which the limiting factor is the supernormal phase. Thus an adequate explanation is afforded for the old observation of Wedensky,[17, 18] who noted that in a fatigued muscle-nerve preparation subjected to tetanic stimulation at a level barely below the threshold, application of a single threshold stimulus was followed by a tetanic response which continued as long as the previously subthreshold stimulus was maintained. In the light of the present work it is recognized that the single effective shock produced a discharge, which was followed by a supernormal period during which the previously ineffective stimulus was capable of evoking a second response, and so on.

The second contribution, implied in work extending over a number of years, but only recently clearly stated, is the demonstration that very similar changes both in threshold and potential follow a single stimulus which is ineffective in producing a propagated disturbance.[19] In the chain of events following such a stimulus only the spike of the action potential and the absolutely refractory period are lacking. The first and second positive afterpotential find representation in coincident increases in threshold, and the negative afterpotential is accompanied by a decrease in threshold.

The first positive potential wave and its accompanying relative refractory period find application in explanation of the Gildemeister phenomenon, in which a single ineffective shock applied to a nerve can render ineffective a second shock following closely after it, even though the second shock alone can be demonstrated to be well above threshold strength. The first shock, although ineffective, had obviously left behind a period of relative refractoriness, which rendered ineffective a

previously effective stimulus. In a similar manner the Wedensky inhibition may be explained.

Recognition of the next phase in the cycle of charges of threshold following a subthreshold stimulus permits an insight into an important physiological phenomenon, loosely termed "summation." It has long been known that during the stage of partial curarization of the myoneural junction a single volley arriving over the motor neuron may prove ineffective, while two volleys, even though fairly widely separated, evoke a response in the muscle. A similar phenomenon has been shown to exist in an isolated nerve trunk, usually over a shorter temporal course, although in certain abnormal conditions summation intervals of several hundred milliseconds are discovered. It is clear that the actual stimulus (that is, electrical shock) is of extremely short duration, and at the neuromuscular junction the spike potential of the nerve ending or the quantum of acetylcholine liberated disappear with almost equal rapidity. It is therefore impossible to speak of a temporal summation of subliminal stimuli in any strict sense. Actually, the first subliminal stimulus, although it quickly disappears, evokes a reaction in the stimulated area, producing, after a short, relatively refractory period, a period of enhanced excitability during which the second, normally subthreshold, stimulus is now effective. It may well be that the second stimulus too is ineffective, but it is in turn followed by a somewhat greater depression of threshold during which a third stimulus is capable of initiating a propagated discharge. There can be little doubt that this concept will prove of the greatest value in all applications of what now must appear to be an inappropriate term: "temporal summation."

Humoral Transmission at the Myoneural Junction

The third major advance in knowledge of the physiology of nerves and muscles lies in the application to skeletal neuromuscular transmission of a concept previously applied in the autonomic system to account both for transmission at the synapse between preganglionic and postganglionic neurons and the mediation of the action of the postganglionic activity on the effector systems. Sir Henry Dale, who with his co-workers is largely responsible for this newer concept, has called attention to the fact that DuBois-Reymond[20] had suggested that nerves may act to stimulate muscles by liberating at their endings in the muscle a quantum of a chemical substance which is the direct stimulator of muscular activity. The various steps in the development of the subject since then have also been traced in recent publications by Sir Henry Dale.[21] Their culmination in the discovery by Loewi of a chemical transmitter, later shown to be acetylcholine, in parasympathetic activity and of a sympathetic transmitter resembling adrenalin by Cannon must be classed with the most important physiological discoveries of the century. More recent have been the postulation of an acetylcholine transmission at the synapses in autonomic ganglia, largely through the work of Dale, and lately the claim has been advanced that at the motor end plate of skeletal muscles an acetylcholine transmission also occurs.[22–25]

Naturally these claims have not met with universal acceptance, and adherents are still to be found to the theory that the spike potential of the nerve ending in the muscle constitutes the stimulus to muscular contraction.[26] An examination of material presented on both sides of the controversy reveals that both theories fail to satisfy all the criteria of rigorous proof, of which the following may be mentioned.

Is the theoretical transmitter present at the synapse at the time of transmission? Obviously the spike potential of the nerve ending must be present, although it has of course never been recorded. Acetylcholine can be detected in perfusates, but does not begin to appear for several minutes after stimulation begins. Obviously the perfusion technic cannot provide the essential proof of accurate time relations. It fails to prove that the material recovered actually originates in the synapse, and Lorente de Nó[27] claims that in fact nonsynaptic tissue gives as much acetylcholine as do synaptic regions. Of course action potentials are also found in synaptic and nonsynaptic regions.

Both acetylcholine and rapid electric shocks—more specifically spike-action potentials—are known to stimulate muscles when properly applied. So, however, do a great many other substances. Potassium ions, which may well play a part in transmission, are particularly excellent stimulators. Evidence that acetylcholine when injected into muscles causes all-or-nothing contractions cannot therefore be considered as more than presumptive evidence, which already exists in equal strength for electrical transmission.

It seems therefore that evidence for chemical transmission can be balanced by equally weighty, yet equally inconclusive, evidence for electrical transmission, and that a decision cannot be made at this time.

Smooth Muscle

Valuable contributions have recently been made to this hitherto neglected field in physiology by the studies of Rosenblueth and collaborators,[28, 29] by Eccles and a co-worker,[30, 31] and by Fletcher.[32, 33] Study of their work reveals primarily how little really is known of the physiology of smooth muscle. Save only for the work of McSwiney,[34] almost nothing is known of the nature of the sim-

ple muscle twitch of smooth muscle. The identity of the smooth muscle "motor unit" is equally unknown, as are the parts played by contraction of the twitch and tetanus type, and by contracture in producing tension in various smooth muscles. Whether the basic syncytium is of physiological importance and how far it accounts for co-ordination of contraction are subjects only for conjecture. What is more surprising, it is impossible to find agreement concerning the presence of a spike-action potential characteristic of propagated disturbance in smooth muscle. The well-recognized presence of a spike potential in active cardiac muscle, and the careful analysis of the potential waves found by Eccles, seem to indicate that at least in the smooth muscle which he studied, the retractor muscle of the nictitating membrane, a spike potential exists. Incidentally, Eccles was able to record long-lasting (200-millisec.) negative potentials in this muscle following subthreshold volleys via its motor nerve, and demonstrated that during this period summation of a second individually inadequate volley was possible. Much basic work on smooth muscle will probably follow these very stimulating investigations.

THE CENTRAL NERVOUS SYSTEM

Nature of the Central Processes

Few suggestions have been of more value to physiologists than Keith Lucas's[35] to the effect that phenomena in the central nervous system are susceptible of explanation in terms of events in simple nerve and muscle. Today, with rival theories of neuromuscular transmission dividing physiologists into opposing camps, the genius of Lucas is more than ever needed to point the path to those who venture into the central nervous system. The evidence which Dale and his collaborators have accumulated in favor of synaptic transmission has been largely concerned with the transneuronal transmission in sympathetic ganglia, in which but a single synapse is involved, but which shows many of the characteristics of transmission within the spinal cord. These workers have carefully avoided any attempts to extend their theory to the central nervous system, in the absence of strict proof. Recently Wright and others[36–38] have clearly shown that acetylcholine, eserine and adrenalin, all implicated in humoral transmission in peripheral structures, have no less striking effects on reflex activity in the cord. They too, however, emphasize that the evidence they present need only indicate a pharmacologic effect having no necessary relation to the normal physiology of reflex activity. The recent paper of Lorente de Nó,[27] calling in question the essential evidence upon which Dale's work is based, serves to emphasize the very tentative state of all theories at present entertained.

The work of Gasser on the excitability changes following propagated discharges and subliminal stimuli is on the other hand being applied with increasing success to interneuronal transmission. The most profitable application has been the elucidation of the central excitatory state of Sherrington as the period of lowered threshold following a subliminal stimulus, and the central inhibitory state as in all probability a manifestation of the period of increased threshold following a subliminal stimulus. The independent work of Eccles[39] and Lorente de Nó[40] indicates that in the central nervous system a distinction between "temporal" and "spatial" summation must be made, as it can be in peripheral nerves. Thus the effects of a simultaneous discharge of several "boutons" or synaptic endings is brought about by a true "spatial" summation of the stimulus produced by each, whether electrical or chemical. Repeated volleys over the same endings must, however, be separated by an interval no less than the absolutely refractory period of the ending, with the result that the voltage of the spike, or the quantum of acetylcholine, has disappeared by the time the second stimulus arrives. In such circumstances the resulting discharge is in reality brought about by the lowering of threshold which invariably follows a subliminal stimulus.

Application of the study of action potentials to the central nervous system presents difficulties identical with those faced by earlier electrocardiographers, amplified many fold: (1) the necessity for indirect leads; (2) a complicated system of action potential production; and (3) the serving of only a small proportion of the cells as a pacemaker, with functional communications on a wide scale. For this reason the analysis of electrical charges in the central nervous system is still incomplete. Those of the spinal cord are naturally more simple but even they present great difficulties. Even so, the presence in cord potentials of the usual spike and afterpotentials are to be recognized, and the association with them of threshold changes is determined.

The analysis of brain potentials by Davis and his collaborators in Boston[41] and by Adrian[42] in England has served to introduce a subject which still remains in great confusion. The recent authoritative review by Jasper[43] should also be consulted.

Central Representation of the Autonomic System

The original hypothesis as proposed by Bichat to account for the activity of the autonomic nervous system attributed to that system complete independ-

ence of the central nervous system, and located the source of spontaneous activity and the center for reflex behavior in the peripherally situated ganglia. While some modern work, notably that of Schwartz,[44] suggests that reflexes may possibly take place in ganglia isolated from the central nervous system, the bulk of evidence suggests most strongly that representation of the autonomic system is to be found side by side with that of the skeletal nervous system at each level of integration. Spinal autonomic reflexes have in fact been reported, and the decerebrate animal possesses many notable autonomic reflexes. Further representation in the hypothalamus has been recognized for a number of years, and Ranson's[45] Harvey Lecture for 1937 summarizes this subject from the viewpoint of one of its most active students.

It is no less certain that the autonomic system is well provided with cortical representation. The recent review by Fulton[46] indicates that cortical representation had in fact been suspected by a great number of the best neurologists of the nineteenth century, but the experiments which they carried out failed to meet all the criteria of rigorous proof. Within the past few months definite, unequivocal evidence of cortical representation has been provided by the work of E. C. Hoff and Green.[47, 48] Rigorously excluding changes produced by spread of current and due to reflexes originating in the movements of skeletal muscle, these investigators were able to demonstrate the presence of sharply circumscribed areas whose stimulation produced changes in blood pressure, heart rate and capacity of the vascular bed in the kidney and leg. Both the motor and premotor areas contained motor point, and very closely located spots often gave diametrically opposed results. Rioch and his co-workers[49] and Schwartz[50] furnish corroborative evidence. Further evidence of the close functional interrelation between the centers of autonomic and skeletal reflexes is provided by the observations of Dusser de Barenne and Ward,[51] Schweitzer and Wright,[52] and Barclay and Franklin,[53] who independently demonstrated the effect of somatic reflexes of afferent stimulation normally associated with autonomic reflexes. The postural changes associated with micturition in animals are of course obvious examples of this close interaction.

THE CARDIOVASCULAR SYSTEM

Intraventricular Conduction

For years the classic description by Lewis of the spread of the cardiac impulse through the ventricles has taught that the impulse is propagated at a rapid rate in the bundle of His and Purkinje fibers to the endocardial surface of the ventricles, where a transition to muscle fibers takes place and a much slower conduction outward to the epicardial surface occurs.

Objections to this hypothesis were first raised by Robb[54] in her careful anatomical studies of the distinct muscle bundles of which the heart is composed. She suggested that just as each bundle has its own blood supply, and suffers as a unit from obstruction to that supply, so also it is activated by its own Purkinje supply. The spread of the cardiac impulse must therefore be considered to consist of a rapid spread along the Purkinje system to a muscle bundle, and from there along the bundle by direct conduction along muscle fibers, as in the auricle, at a rate not much less than that in the Purkinje system.

Somewhat later, several workers found unmistakable proof that the Purkinje system extended beyond the subendocardial network, throughout the entire myocardium.[55, 56] This extension of the Purkinje system, which in fact had not entirely escaped the notice of earlier histologists, provided the incentive to a renewed study of the spread of the impulse through the ventricle, with the use of more adequate recording systems, and avoidance of cooling and drying of the surface of the heart. These studies[57, 58] have shown fairly conclusively that the impulse does arrive first at the septum, and the region of the ventricular walls near the septum, as demonstrated by Lewis. It is obvious also that the entire heart, both internally and externally, is then activated very rapidly, and that no differences can be found between the inside and outside. Finally, no evidence can be found to support Robb's suggestion that the process of excitation follows muscle bundles. It can thus be concluded that the intramuscular Purkinje network acts to distribute the cardiac impulse, with great rapidity, to all parts of the myocardium, rather than to the endocardial surface of the ventricles, as was formerly believed.

The Blood Supply of the Myocardium

A second fundamental contribution to the knowledge of the heart is recognized in the studies of Wiggers and his associates on the blood supply of the myocardium. Recent anatomical investigations, well reviewed by Wearn in Levy's *Diseases of the Coronary Arteries and Cardiac Pain*,[59] have indicated that blood entering the coronary arterioles may take widely differing courses to the right ventricle. Some, of course, may pass into capillaries and thence by way of the venules into the coronary sinus and right auricle. The well-known Thebesian channels may divert some blood from the capillaries and venules directly into the right ven-

tricle. It is now recognized that accessory passages, the arteriosinusoidal and arterioluminal vessels, also exist between the arterioles and the ventricular chambers.

Some of the physiological implications of these facts have been recognized for many years, and while it is known that under certain conditions approximately 70 per cent of the coronary flow returns through the coronary sinus, physiologists have found that the actual proportions may vary widely. In fibrillating hearts especially, the Thebesian outflow was found to predominate. This led to the supposition, now carefully worked out by Johnson and Wiggers,[60] that right ventricular pressure is a major factor in diverting blood from the Thebesian channels to the coronary sinus. Johnson and Wiggers now report the following important conclusions: (1) the coronary sinus normally empties into the right atrium only during systole; (2) increasing the right ventricular pressure causes a proportional increase in coronary sinus outflow, all other factors remaining constant; and (3) the increase in coronary sinus outflow produced by certain drugs and by stimulation of cardiac nerves may well be the result of slight elevation of right ventricular pressure. It is more than ever obvious, therefore, that the measurement of coronary sinus outflow, taken by itself, cannot be used as a method for estimating the amount of coronary circulation or the variations it may undergo.

To the question of how coronary flow may be measured, Johnson and Wiggers[60] have devoted great perseverance and the most exquisite technics. The present studies, well reviewed in the chapter on coronary flow written by Wiggers for Levy's *Diseases of the Coronary Arteries and Cardiac Pain*,[59] are based principally upon the determination of the velocity of blood flow by the method of Pitot's tubes, in which the velocity is calculated from the differential pressure between two tubes inserted into a vessel, one directed against and one with the circulation. The most interesting outcome of this method to date is the confirmation of the finding of Anrep that the flow of blood may slow or even stop momentarily during the brief isometric phase of systole, coupled with the demonstration that despite this momentary stoppage, as much or more blood may flow out of the coronaries during systole as during diastole.[60]

The Action Potentials of the Myocardium

The identification of the multiple phases of the monophasic action potential in nerve fibers carries with it the important implication of application to other tissue producing action potentials. Of all such tissues perhaps the heart is most interesting, and presents the most difficulties. Much remains to be learned: the nature of the monophasic action potential has become the subject of renewed study,[58, 62, 63] and the manner in which local potentials summate to produce the electrocardiogram as derived from external leads continues to be debated.[62, 64, 65]

Especially interesting have been the successful attempts of Rothberger and Goldenberg[66–70] to register monophasic action potentials from isolated strips of Purkinje fibers. These strips, which beat rhythmically, show a monophasic action potential of at least two phases, a spike and a negative after-potential. Slow changes from positivity to negativity are occasionally detected immediately before the spike of spontaneous discharges.

Simultaneous mechanograms prove definitely that the electrogram does not terminate with the end of mechanical events, but persists for some time after, and varies independently of mechanical events under the influence of a variety of conditions. This suggests that the association of the end of the T wave in the electrocardiogram with the end of systole is neither exact nor of any significance.

These studies have offered a new approach to a problem that has long agitated physiologists: the origin of the so-called "ectopic" arrhythmias, including extrasystoles and tachycardias from both auricles and ventricles. There has been a growing tendency to consider these as the result of "reentrant excitation" from a wave traveling continually in a circle in the cardiac tissue. While this hypothesis successfully accounts for auricular flutter and fibrillation, its extension to the extrasystolic arrhythmias has been vigorously opposed by those who favor the hypothesis that these irregularities are brought about by the development of an ectopic pacemaker, which gives rise to a single beat, a short burst of tachycardia, or a long run of tachycardia, depending upon the degree to which its rhythmicity surpasses that of the normal pacemaker and the persistence of this change.

In favor of circus movement has hitherto been the phenomenon of "coupled beats" or "bigeminus," in which an extrasystole alternates with a normal beat. It was noticed that the extrasystole was in some way coupled with the preceding beat; if the rhythm of the normal beat was altered, that of the extrasystole likewise changed, and to the same degree. It was thought that the normal beat set up a circus movement in the heart, which after traversing some undesignated pathway, emerged to stimulate the heart and provoke the premature beat.

The Viennese workers, finding that isolated strips

of Purkinje fibers produced action potentials having many of the characteristics of nerve fibers, recalled that the work of Gasser and Erlanger had solved the mechanism of a phenomenon discovered long before by Wedensky. As mentioned before, this worker had noticed that a frog's motor nerve, on being stimulated tetanically at a subthreshold level, responded to a single effective shock, not by a single twitch but by a tetanus, which persisted as long as the previously subthreshold stimulus was maintained. It became obvious that the preparation must have been one showing a marked supernormal phase after recovery from the refractory period of the single shock. During this period the previously ineffective tetanic stimulation evoked a response, likewise followed by a supernormal phase, and so on. It was then found that in isolated Purkinje strips the coupled beat occurred just at the height of the supernormal period following the first beat. This work suggests that just as a marked supernormal period in the nerve is found to favor the appearance of tetanic discharge, so also in the heart a supernormal period forms the basis for the development of ectopic arrhythmias of all types. Certainly these observations convert a cogent reason for believing in the circus movement into very much more valid evidence for the ectopic pacemaker theory. While the importance of these experiments and the inferences to be drawn from them are obvious, the presence of supernormality in the intact mammalian heart remains to be adequately explored. Only then can the significance of the present studies be determined with accuracy.

Physiology of the Veins

Study of the physiology of the veins has received renewed impetus in the publication of Franklin's[71] *Monograph on Veins.* The volume reflects not only the important contributions he has made to the subject through a series of investigations extending over many years, but also a deep interest in the history of the circulation, so well manifested in his translation of Lower's *Treatise on the Heart.* Another individual contribution worthy of note is the demonstration by Nonidez[72] of the presence of receptor organs in the intrapericardial parts of the great veins. Both the venae cavae as well as the pulmonary veins are shown to be richly supplied with subendothelial endings greatly resembling the pressor-receptors in the carotid sinus, the aorta and the right subclavian artery. Endings of a different type were found around the muscle fibers in the walls of the pulmonary veins and superior vena cava. The first were assumed to be the receptor organs for the reflex first described by Bainbridge, who found that increase in the pressure within the right auricle evoked a reflex acceleration of the heart. No function has been ascribed to the perimuscular terminations.

RESPIRATION AND METABOLISM

Nervous Control of Respiration

The role of the carotid body in the regulation of respiration was anticipated many years ago by Siciliano,[73] who occluded the great arteries of the neck and observed both changes in blood pressure and alterations in rate and depth of breathing. He clearly stated his belief that the region of the common carotid near the bifurcation might prove to be an important point of origin for reflexes regulating the blood pressure and respiration. It is only recently, largely through the work of Heymans, that the carotid body has been recognized as a center specifically stimulated by anoxia. The most recent development in this field has been the discovery that certain drugs act to stimulate respiration by virtue of a local action on the carotid body.[74, 75]

The location of the "respiratory center" has interested physiologists ever since Legallois found that damage to the medulla was followed by arrest of respiration. Since then attempts to delimit more exactly the areas involved have employed such methods as local warming and cooling,[76] application of drugs to discrete areas and the production of small, circumscribed injuries. All these methods have failed to indicate that any specific group of cells in the medulla is the pacemaker of the respiratory center. More recently the method has been introduced of obtaining action potentials through small electrodes inserted into various parts of the medulla.[77–79] These have shown that cells in a number of the nuclei of the medulla discharge rhythmically in synchrony with discharge of the motor neurons of the respiratory muscles, and that to none of them can as yet be ascribed the function of pacemaker. Just as the precise location of the pacemaker of the heart depended upon the determination of the point of primary negativity, so it would seem that the position of the respiratory pacemaker depends upon the exact timing of the moment of discharge of one group of cells as compared with the others.

The Intimate Nature of Cell Respiration

Recent years have seen the development of a new approach to the problem of the intimate nature of cell and tissue respiration, namely the development of instantaneous methods of assaying changes in the interior by color or spectroscopic changes. The determination by Keilin in 1925 of the time of reduction of cytochrome as observed visually in a spectroscope was followed by the use of photoelectric cells for study of similar activity in yeast

by Haas in 1934. Optical changes in contracting muscle were recorded photoelectrically by von Muralt in 1934. Last year Millikan[80] reported the measurement of the reduction of muscle hemoglobin in intact muscles, using a photoelectric cell to pick up changes in color of the muscle illuminated transversely. The system was made stable to a variety of possible variants such as thickness of muscle, amount of contained blood and the changes in opacity noted by von Muralt, by utilizing only the change in transmissibility of green and red light brought about by reducing or oxidizing muscle hemoglobin. Millikan concludes from these experiments: (1) muscle hemoglobin acts as a short-time oxygen store to tide the muscle over from one contraction to the next; (2) when contraction takes place the oxygen demand starts to rise in less than 0.2 seconds, reaches its maximum value within 1 second, and falls nearly to its resting value within 10 seconds of the end of the contraction; (3) blood flow through the soleus muscle of a cat appears not to be greatly affected by maximal tetanic contraction, whether the muscle is stimulated directly or by its nerve.

It is too early to attempt to fit information such as this into the general picture of muscle chemistry. It is essential to point out, however, that the accuracy of the time values obtained by such methods is conditioned by the nature of the recording system. The galvanometer used by Millikan to register the changes in current produced by the photoelectric cell was stated to have a period of about one second, a figure out of all proportion to the time relations that undoubtedly occur. This problem has been considered in a second series of experiments designed to answer the question of whether enzymes enter into chemical combination with the substrate.[81–84] Stern[81] had previously shown that when monethyl hydrogen peroxide was added to a concentrated, highly active solution of liver catalase, the spectrum of the free enzyme disappeared and was replaced by two new absorption bands. Much later the new bands faded and the old spectrum reappeared. To measure the rate of the first reaction between enzyme and substrate, Stern and DuBois[82] devised an apparatus in which monochromatic light of the same wave length as the absorption bands to be studied penetrated a cell containing the reaction mixture and struck the cathode of a photoelectric cell. The photoelectric current was amplified and recorded through a string galvanometer. It was found that, while mixing was complete in 0.04 to 0.06 seconds, the time for half completion of the enzyme-substrate reaction varied from 0.06 to 0.26 seconds.

To check the accuracy of these methods, in which both the photoelectric cell and the string galvanometer interposed definite time limitations, these investigators devised a direct method whereby the reaction cell was placed between the light source and the slit of the spectrograph, which was equipped with a falling-plate camera, so that continuous pictures could be obtained of the changes in the spectrum.[83] This method demonstrated first that mixing of the reagents was completed as quickly as 0.006 seconds, and that the enzyme-substrate reaction was completed before mixing was over.

While such promising studies are carried on, study of similar problems by the classic chemical procedures have continued to progress. Some of these have been admirably summarized in a volume of essays entitled *Perspectives in Biochemistry*,[85] published in honor of Sir Frederick Gowland Hopkins on his seventy-fifth birthday. Particularly interesting are the reviews by Needham of the chemical cycles in muscle contraction, and of Szent-Györgyi on his own work on the catalytic action of the four-carbon-atom dicarboxylic acids in cell respiration. His discovery of the function of these acids as a link between the foodstuff and the Warburg-Keilin oxidative enzymes is equivalent in interest to his demonstration that the stages in fermentation involving trioses were followed almost exactly by the four-carbon acids, which were in reality trioses stabilized by the addition of a terminal carboxyl group.

THE ENDOCRINE GLANDS

Glands Regulating Carbohydrate Metabolism

In 1936 this journal published an account of one of the most fruitful advances in endocrinology since the discovery of insulin.[86–87] In his Dunham Lectureship Series, delivered at the Harvard Medical School in 1935, Houssay described a long series of experiments in his laboratory which showed unmistakably the intimate association between the secretion of the anterior lobe of the pituitary gland and the regulation of carbohydrate metabolism. His evidence consisted of three main points: (1) the great hypersensitivity of hypophysectomized animals to the injection of insulin, and their equally striking lack of sensitivity to the injection of adrenalin; (2) the improvement in the condition of depancreatized animals effected by removal of the hypophysis; and (3) the production of persistent diabetic-like states by the injection of anterior pituitary preparations.

These experiments, amply confirmed, made necessary a revision on a wide scale of previous notions concerning the mechanism involved in production of diabetes mellitus in man. It could no

longer be held that this disease was invariably of pancreatic origin, and that varying degrees of insulin deficiency resulted in varying degrees of impairment of the ability of the tissues to utilize glucose, terminating ultimately in total inability to oxidize it. It also became obvious that processes might exist under hormonal control that result in glucose production from noncarbohydrate sources, and that other hormones might act to increase or decrease carbohydrate utilization.

Recently the role of other endocrines in regulating carbohydrate metabolism has been extended through the work of Long and his colleagues.[88, 89] Removal of the adrenal cortex in cats, and maintenance of the animal over long periods by administration of potent preparations of cortin, permitted Long to ascertain: (1) that adrenalectomy improves the total pancreatic diabetes to the same degree as does hypophysectomy, and causes a prompt disappearance of glycosuria in partially depancreatized rats; (2) that injections of extracts of the anterior pituitary fail to produce glycosuria in adrenalectomized rats; and (3) that the adrenalectomized rat shows a sensitivity to insulin due to cortical loss as well as the medullary deficit.[90] The only failure in the almost exact parallel between the removal of the adrenal cortex and the anterior pituitary is that cortical extracts which are potent so far as water and salt metabolism are concerned fail to restore glycosuria in a depancreatized, adrenalectomized animal to the degree that anterior pituitary extracts prove effective in hypophysectomized, depancreatized animals. However, enough evidence has been accumulated to indicate that the adrenal cortex plays an important part in sugar metabolism, both in normal and in diseased subjects.

The Sex Hormones and Growth-Promoting Agents

The appearance in 1937 of a second edition of Fieser's[91] *The Chemistry of Natural Products Related to Phenanthrene,* a year after its first publication, indicates the enormous interest in these compounds. Elucidation of close relation between compounds which produce cancer and the internal secretions of the sex glands is of the greatest interest both to physiologists and to physicians. The retardation of the growth of certain tumors brought about by suppression of ovarian secretion has been known to clinicians for some time, and Allen[92–95] is largely responsible for the demonstration that injection of follicular hormone in male or female mice will produce mammary cancer in susceptible strains. What is more interesting, cancer has at times been produced in regions other than in the mammary gland, where it is usually observed. The discovery of the chemical similarities between the cancer-producing substances and the sex hormones places these studies upon a rational basis, and forms the starting point for future work on the physiology of normal and abnormal growth.

One of the most recent developments in this field is the study of the effect on cell growth of the well-known substance of this group, colchicine.[96] This drug, recognized for a great many years as a sovereign remedy for the gout, is now found by Lits to have a marked inhibitory effect on cell division in animals when injected in certain concentrations. What is more surprising, it seems to have its specific effect only at the metaphase stage of cell division. It becomes therefore a new and valuable method for studying rate of growth in a variety of conditions, since cells accumulate in metaphase from the time of injection to the time of sacrifice. Whether the growth-arresting property of colchicine has any relation to its effect in gout is at present a matter only for conjecture.

A noteworthy study in another field of endocrinology is that by Gilman and Goodman.[97] They have been able to detect the presence in the urine of the pituitary antidiuretic hormone, and to demonstrate that it is secreted in response to a demand for water conservation.

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

ANTEMORTEM AND POSTMORTEM RECORDS AS USED IN WEEKLY CLINICOPATHOLOGICAL EXERCISES

FOUNDED BY RICHARD C. CABOT, M.D.

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CASE 24231

PRESENTATION OF CASE

First admission: A thirteen-year-old, native-born, white boy entered the hospital with the complaint of lameness of two years' duration.

Seven years before entry he developed polydipsia, frequency and severe enuresis. He was admitted to another hospital two years later, where physical examination revealed slight enlargement of the heart and a blood pressure of 120 systolic, 85 diastolic. At that time his phenolsulfonphthalein test of renal excretion gave 10 per cent in the first hour and a total of 20 per cent in two hours. The nonprotein nitrogen of the blood was 75 mg. per cent. An Addis determination of urine content showed a specific gravity of 1.012, a trace of albumin, 1,350,000 casts (upper limit of normal 10,000) and 500,000 red cells (upper limit of normal 600,000). After forcing fluids for ten days the nonprotein nitrogen was 26 mg. per cent. About that time his physical development began to slow down, and during the two years before entry his height remained stationary. During the year after his entry to the other hospital there was no great change in his condition. His blood pressure remained below 108 systolic, 70 diastolic. The urine showed rare red-blood cells and granular casts, and on one occasion the nonprotein nitrogen of the blood was 56 mg. per cent. Three years before entry to this hospital he had a mild attack of scarlet fever, and after a month of convalescence in bed began to have difficulty in walking and supporting his weight. There was associated dyspnea on exertion and easy fatigue. He also complained of pain in the lower lateral chest, bilaterally, which was aggravated by laughing or sneezing. His physical disabilities gradually progressed, until he was almost unable to climb stairs without support; and he began to use a walking stick. He was taken out of school from the fourth grade which he had had to repeat because of poor reading ability. At no time did his muscles appear to be larger than normal but rather appeared to decrease in size as his weakness progressed. He never had an exaggerated lordosis, but he developed a waddling gait and a bilateral valgus deformity of the knees. Two years before entry he had an attack of cramps in both hands and feet lasting half an hour, with recurrence of the foot cramps at monthly intervals for three to four months. Occasionally his hips were sore, and shortly before entry he complained of painful stiffness in the joints of his little fingers. About nine months before entry his skin became coarse and dry, and his hair became thinner. He was seen in the outpatient department at that time, and a neurological examination revealed no significant findings except muscular atrophy and weakness with diminished to absent tendon reflexes. There was no characteristic distribution of weakness, and he was considered to present a problem of general deferred growth. His urine had a specific gravity of 1.004 and contained a slight trace of albumin, and the test for sugar gave a green reaction with sediment.

For many years he had had frequent sore throats until his tonsils and adenoids were removed five years before entry, which was two years after the onset of his illness. He had had whooping cough at the age of five, chickenpox at nine and measles at ten, shortly after his attack of scarlet fever. His physical and mental development had appeared to be normal up to the onset of his illness. He had had no visual symptoms, epistaxis, orthopnea, jaundice, melena, hematemesis, hematuria, dysuria, edema, puffiness of the face or any neurological symptoms, such as twitching or convulsions. His family history was negative except that his maternal grandmother had mild diabetes.

Physical examination revealed an undernourished, underdeveloped boy. The skin was dry and coarse, and there was generalized muscular atrophy and weakness. The tendon reflexes were increased in activity, but neither a Chvostek nor Trousseau sign was present. A forceful apex heart beat was felt in the fourth interspace, 6 cm. from the midsternal line. The heart sounds were of good quality, and no murmurs were heard. The blood pressure was 120 systolic, 88 diastolic.

The temperature was 100°F., the pulse 128. The respirations were 28.

The urine was acid, had a specific gravity of 1.004 and contained the slightest possible trace of albumin, no sugar, 1+ acetone, many coarse granular casts and occasional red cells and white cells. The urine concentration test gave a maximum specific gravity of 1.006. The blood showed a red-cell count of 3,200,000 with 75 per cent hemoglobin, and a white-cell count of 9000 with 76 per cent polymorphonuclears. A phenolsulfonphthalein test of renal function gave 2 per cent excretion in two hours. The nonprotein nitrogen of the blood was 67 mg., the sugar 59 mg., the calcium 7.45 mg., the phosphorus 6.76 mg. and cholesterol 187 mg. per cent. The carbon-dioxide combining

power was 29.3 vol. per cent, and the blood chlorides were equivalent to 100 cc. of N/10 sodium chloride. The basal metabolism rate varied from +7 to +18 per cent. An electrocardiogram showed a tendency to left-axis deviation and low T waves.

X-rays of the bones showed generalized decalcification with widening of the growing epiphyseal lines and some irregularity of the metaphyses. In the upper ends of both fibulas, and in at least three metatarsal bones there were thin fracture lines with some increased density about them, so-called *Umbau*-zone. The sella turcica appeared normal, and the skull was normal in size and shape. Dental films showed absence of the lamina dura in most of the teeth, and retardation of dental development. The chest x-ray was negative; and flat films of the abdomen, though somewhat unsatisfactory, showed no gross calculi or other abnormalities.

He was given a high-carbohydrate, high-vitamin and low-protein diet, with calcium lactate and sodium gluconate. His fluid intake and output were very high, and he used a good deal of table salt with his meals. On the eighth day the nonprotein nitrogen of the blood was 62 mg., the calcium 8.17 mg. and the phosphorus 4.04 mg. per cent. The phosphatase was 12.76 Bodansky units. The chlorides were equivalent to 94 cc. of N/10 sodium chloride. The carbon-dioxide combining power was 56.9 vol. per cent. Eight days later a retrograde pyelogram showed a normal left ureter and kidney pelvis, and no evidence of calcification in either kidney. He was discharged on the eighteenth day essentially unimproved.

Final admission (eight months later). He was followed in the Out Patient Department. Two months after discharge his blood pressure was 118 systolic, 80 diastolic, and he was doing fairly well. Four months before entry the nonprotein nitrogen of his blood was 65 mg., the calcium 6.92 mg., the phosphorus 4.06 mg., the uric acid 5.7 mg. and the sugar 130 mg. per cent. The carbon-dioxide combining power was 25.8 vol. per cent, and the chlorides were equivalent to 94 cc. of N/10 sodium chloride. His appetite gradually became worse, and he lost a little weight. Four days before reentry he began to vomit and continued to vomit all food and fluids taken.

Physical examination revealed an emaciated, lethargic boy showing marked evidence of dehydration. Otherwise the physical examination was essentially the same as before. The heart was apparently not enlarged, and the blood pressure was 118 systolic, 74 diastolic.

The temperature was 98.6°F., the pulse 96. The respirations were 24.

The urine had a specific gravity of 1.005 but was reported otherwise negative. The blood showed a red-cell count of 4,500,000 with 60 per cent hemoglobin, and a white-cell count of 29,000 with 91 per cent polymorphonuclears. The nonprotein nitrogen of the blood was 102 mg. per cent and the carbon-dioxide combining power was 19.9 vol. per cent.

He died on the day of entry.

X-Ray Interpretation

Dr. George W. Holmes: The most striking finding is the decalcification shown in all bones examined, with a widening of the epiphyses which is characteristic of rickets. This is the bilateral line of diminished density with increased density around it, which was interpreted as fracture. It seems to me rather odd that it should be so symmetrical. I wonder if it is anything else. If it is not fracture, I do not know what it is. In the examination of the urinary tract the kidney outlines are rather faintly visible and seem to be quite small for a child of that size. I do not suppose one is justified from the x-ray examination alone in saying definitely what size the kidneys are, but one can sometimes make an intelligent guess as to whether they are large or small, and in this instance they appear to be small. There is no evidence of calcification in the kidneys. In the chest we see the same decalcification of the bony thorax that we see in other places, and a rather high diaphragm. In the lung fields the markings are quite prominent. The heart is perhaps a little enlarged to the left, but might not be abnormal. I should be inclined to think that Dr. Mallory would find that the heart weight was normal. There are no mediastinal masses — nothing in the chest to account for the dyspnea.

Then in the skull the anterior sutures are closed, which is unusual for a child of this age and may mean early closure; the posterior sutures are quite indistinct. In the teeth there is some retardation of growth and change in the peridental membrane. I should not be certain that it is absent. It is a definite sign. I am sure it is found in parathyroid disease, but I am not certain that it is not sometimes found in other conditions. My feeling in this case is toward renal rickets rather than parathyroid disease.

Dr. Harold L. Higgins: What is his age from the epiphyses?

Dr. Holmes: I cannot tell accurately enough

to allow me to decide whether there is late development.

Differential Diagnosis

Dr. Alfred Kranes: This is a very interesting and unusual story, and I think there can be very little doubt that we are dealing with a patient who had renal rickets. The clinical story should be discussed in two phases: (1) the renal disease and (2) the skeletal disease — each one of which might better be considered independently.

The story is unusual because this patient came under observation two years after the onset of his first renal symptoms, and at that time the first accurate observations that were made showed that he did have a moderately severe degree of renal impairment with an elevated nonprotein nitrogen in the blood and a low specific gravity of the urine. Nevertheless, he managed to live for five additional years — a rather unusual survival period after renal insufficiency manifests itself.

It is always more or less of a guess as to what the renal lesion will be when presented with a case of nephritis. In this patient we are simply given a problem in renal insufficiency. We have absolutely no data on which to predict what type of lesion will be found. We have to rely mainly on probabilities. With the disease beginning at his age one has to think of congenital lesions of the urinary tract, the two most common of which are congenital hydroureter — for which there seems to be no evidence in the retrograde pyelogram — and polycystic kidneys — for which we also have no evidence, no abdominal masses having been palpated and the pyelogram showing no enlargement of the kidneys. Both these diagnoses seem rather unlikely. Another type of chronic renal disease in children which may lead to renal insufficiency is chronic pyelonephritis. However, there are no signs of infection, no pyuria has ever been found, and there are no chills or fever, except for one isolated temperature of 100°F. With as little evidence as is present here one can safely exclude chronic pyelonephritis.

We are left, then, with the diagnosis of chronic glomerulonephritis: first, by exclusion and, secondly, because statistically it is the most common lesion at this age. This boy was not seen at the onset of his disease — at least no observations are recorded on him then — so that we do not know whether hematuria was present at the onset. It is frequently overlooked at the beginning of the acute nephritis, at least in the history. However, when he was observed two years later, at which time renal failure was present, hematuria was not found. In addition, his kidneys, as Dr. Holmes mentioned, seem to be very small by x-ray, which would lead me to believe that he did have a very small, contracted pair of kidneys, the result of chronic glomerulonephritis, and that the patient died in uremia.

There is one other possibility, in view of the bone disease, which we have to mention and consider seriously: that is hyperparathyroidism, which will cause chronic renal disease and will also produce the changes that have been described in the skeleton. He had a very high blood phosphatase, although the remainder of the blood chemistry is atypical for hyperparathyroidism. We must remember, however, that the presence of severe renal impairment might mask the characteristic blood findings of hyperparathyroidism, particularly the phosphorus level. I think it is very unlikely that this patient had primary hyperparathyroidism. In the first place the statement is definitely made that there was no calcification in the kidneys, and the renal insufficiency of primary hyperparathyroidism is produced by a process called nephrocalcinosis, or deposits of calcium in the renal tubules which frequently show up by x-ray. Secondly, we have evidence that the renal disease started long before the bone disease, which is quite the reverse of hyperparathyroidism. One would have to have long-standing parathyroid hyperplasia to produce chronic renal insufficiency. Nevertheless, I do believe that this patient's parathyroid glands will very probably be enlarged, not because of but rather the result of prolonged renal insufficiency. We know that in chronic nephritis there frequently is enlargement of the parathyroid glands, and this patient with a renal insufficiency of at least five years' duration, and probably more, ought to have a good deal of enlargement.

We might speculate as to the cause of that enlargement. If one believes, and there is considerable reason for doing so, that one of the primary functions of the parathyroid hormone is to lower the renal threshold for phosphorus excretion, we can then explain the parathyroid hyperplasia as the result of phosphorus retention. The parathyroids become hyperplastic in an effort to reduce the phosphorus concentration of the blood. That such a mechanism was operating here seems likely, because, although this patient had a severe degree of renal damage, the phosphorus content of the blood was only slightly over 4 mg. That I think would be quite unusual in the absence of parathyroid hyperplasia. It ought to be 6, 7 or perhaps 8 mg. per cent. Dr. Albright and Dr. Drake did some interesting experiments here several years ago on the production of parathyroid hyperplasia by the parenteral injection of phosphates into rabbits. They found that by keeping the blood phosphorus

constantly elevated they were able to produce parathyroid hyperplasia. Similarly in this case, if parathyroid enlargement is found, it will probably be secondary to the renal disease and phosphorus retention.

As regards his bone disease which has been described as renal rickets, — undoubtedly a poor term, — the bone changes that these patients have are not really those of rickets. Histologically they are osteitis fibrosa cystica — the same as in hyperparathyroidism; but the term "rickets" has been used for so long that it seems to be here to stay.

What the skeletal changes are due to, is again a matter of great controversy. There are three possible explanations for them, but which one is responsible, or whether all three are, has not yet been settled. The most obvious explanation — that the parathyroid enlargement and hyperplasia produce the skeletal abnormalities — has not found any experimental support. Several years ago a case similar to this in an adult was studied on the wards here, and it was found that the renal excretion of calcium, which in real hyperparathyroidism is much increased, was only slightly elevated. If the parathyroids were responsible for the skeletal changes, one would expect a marked increase of urinary calcium. However, in the case that was studied here, the urinary-calcium excretion was relatively normal. Even with damaged kidneys one would expect fairly good excretion of calcium.

The second explanation might lie in the chronic acidosis that these people have. We know this boy had an acidosis for at least eight or nine months, and the probabilities are that he had chronic acidosis all during the period of renal failure. Any long-standing acidosis will produce a picture in the bones which cannot be differentiated from osteitis fibrosa cystica. Bodansky and Jaffe were able to produce the typical picture of osteitis fibrosa cystica in dogs by prolonged administration of ammonium chloride. We have here the probable explanation of the skeletal changes.

A final explanation is the increased phosphorus excretion in the intestinal tract, which results in the precipitation of calcium phosphate. The ingested calcium is therefore not absorbed since it becomes insoluble, and as a result these individuals live on what amounts to a diet markedly deficient in calcium. Which one of these three above-mentioned possibilities is responsible has not definitely been settled, but the most probable is the chronic acidosis theory.

In summary, I should say that this patient had, primarily, a chronic glomerulonephritis, with a small, contracted pair of kidneys, and that he died in uremia. Secondary to the nephritis and phosphorus retention he developed parathyroid hyperplasia, and along with this, because of the prolonged acidosis, he developed the bone picture of osteitis fibrosa cystica. In addition, because of the prolonged course of his renal disease, I think it is quite probable that he had a rather marked degree of generalized arteriosclerosis.

Dr. Tracy B. Mallory: There is one point not particularly emphasized in the summary that would have been obvious if you had seen the child — his dwarfism. His growth was quite markedly retarded. He was short and much underweight as well. Does that in any way alter your feeling?

Dr. Kranes: I think that prolonged renal insufficiency could produce the dwarfism by the same mechanism that the bone changes are produced.

Dr. Harold L. Higgins: I think the cramps could quite well have been due to tetany, as his blood calcium was down to 7.5 mg. per cent most of the time. The boy was 48 in. tall, which is the height of a boy about eight years old. As he was thirteen years and two months old, he was five years behind schedule so far as height was concerned. But his head measured 21 in., which is the average size for an eight-year-old child. He seemed to be a proportional dwarf and not simply a dwarf because of short extremities. The appearance of the skin, which was rather smooth, and the very scanty hair somewhat suggested a pituitary midget; but the general condition of the child was that which we frequently see in children who develop kidney insufficiency. They stop growing and develop what is known as renal rickets, which really is not rickets at all, although it probably is caused by the renal condition.

Clinical Diagnoses

Uremia.
Chronic glomerulonephritis.

Dr. Kranes's Diagnoses

Chronic glomerulonephritis.
Renal osteitis fibrosa cystica.
Parathyroid hyperplasia.
Uremia.

Anatomical Diagnoses

Chronic nephritis.
Healed pyelonephritis?
Cardiac hypertrophy, slight.
Pericarditis, chronic fibrous.
Osteitis fibrosa, slight.
Parathyroid hyperplasia, very slight.
Basophilism of the pituitary.

Pathological Discussion

Dr. Mallory: The relation of renal insufficiency to osteitis fibrosa seems to be very well established, but what relation there is between renal insufficiency and dwarfism is still a very open question. I spent a good deal of time trying to find some information about it in the literature and must admit I had very little luck. We have seen here one case with marked so-called renal rickets, that is, marked fibrotic and cystic changes in the bone, without dwarfism. This case today is somewhat over on the other side. It showed a marked grade of dwarfism and changes in the bone that one can recognize as similar to osteitis fibrosa, but they were very early. Quite to our surprise, the parathyroids were not large. We had fully expected that we would find very big ones, as Dr. Kranes predicted. We were only able to identify three. When all the parathyroids cannot be found it is quite certain that they must be small. Those we did find were barely larger than normal and only with the microscope could one be sure there was some hyperplasia. Similarly, the changes in the bones, though present, looked as if they were of comparatively short duration. So this case on the whole supports the theory of the bone changes' being secondary to acidosis. At least we know that acidosis was present for a considerable period of time. The thyroid and adrenals were perfectly normal. The kidneys were shrunken, and distinctly smaller than normal. At autopsy we thought the ureters were slightly dilated. Their diameter was estimated at 5 mm. which would be large for a child of that age. The largest proportion of cases of renal rickets reported have been in association with congenital dilatation of the ureters. I believe we must add this case to the list, though the anomaly was present only in a very slight degree. It would be rash to try to state dogmatically the exact nature of the renal lesion. It was an end stage of a very chronic process with no evidence of progressive damage at the time of autopsy. There were quite a significant number of perfectly normal glomeruli which would be a little surprising if it were the end stage of glomerulonephritis. Certainly no active glomerulitis was present. The tubules, in contrast, were reduced in numbers out of proportion to the destruction of glomeruli, and the degree of interstitial fibrosis was quite marked. The pelves were not dilated, and sections which included the pelvis showed no signs of inflammation. Certainly there was no pyelonephritis at the time of death. I can conceive of a kidney such as this being the end result of a completely healed pyelonephritis or of interstitial nephritis of the type occasionally seen with scarlet fever, but cannot rule out with certainty a completely burned-out glomerulonephritis.

Dr. Kranes: What about the arteries?

Dr. Mallory: They did not show any great amount of atheromatosis. The heart weighed 175 gm., which would probably be within the normal limits for a boy of thirteen if he were of normal size, but seemed hypertrophic in proportion to the general development.

I found the pituitary very interesting. It was of normal size, but the sections show unusual proportions of the three types of cells. Chromophobes, which normally make up two thirds of the total, were greatly reduced — to about 20 per cent I should guess. Acidophils were relatively and perhaps absolutely increased in number and basophils were unquestionably greatly increased in number, both absolutely and relatively. I should estimate them at nearly 25 per cent of the total. Of course not too much emphasis should be placed on estimates unsupported by an actual count, but the decrease in chromophobes and the increase in basophils are so marked in this case that there can be no doubt that the ratios are very abnormal. In comparison with an adult pituitary these changes are certainly significant. I must confess to knowing little about the child's pituitary, but in view of Parsons's* findings I think we may assume the changes are abnormal for the child as well.

CASE 24232

Presentation of Case

A fifty-two-year-old American businessman was admitted complaining of cramping abdominal pain.

For one week before entry the patient suffered from intermittent cramplike pain in the lower abdomen. The pain was sufficiently severe to cause him to double up and on several occasions morphine was required for relief. Between pains there was a persistent, dull, aching soreness in the lower abdomen, more pronounced on the left side. During the week of illness the temperature ranged between 100 and 102°F. Associated with the cramps there were nausea and vomiting, and the patient was unable to eat very much food. On occasion the pain was accompanied by a "bearing down" sensation and a great urgency to defecate. Throughout the week of illness there were almost constant bubbling and grinding noises in the abdomen.

The patient's stools had always been rather loose

*Parsons, R. J.: The pituitary gland and its relation to age, hypertension and pathological processes: a study of 107 unselected pituitaries. *Medical Papers Dedicated to Dr. Henry A. Christian.* Baltimore: Waverly Press, Inc., 1936. Pp. 366-405.

in consistence and for about fifteen years he had had three to six watery bowel movements daily. Since the onset of the current attack the frequency increased, but the amount of each movement became scanty. The stools never contained pus or blood. There was no loss of weight.

About three years before coming to the hospital the patient had had an attack of pain similar to the present illness. At that time there were nausea, vomiting, fever and frequent, small stools. On occasion since then there had been brief twinges of lower abdominal pain lasting for a day or two.

Physical examination showed a well-developed and nourished man in no acute distress. The pupils were equal and reacted normally to light. The lungs were clear. The heart was normal. The blood pressure was 125 systolic, 80 diastolic. The abdomen was full and soft. No spasm was elicited. A smooth, slightly tender, baseball-sized mass was palpated in the left iliac fossa. It appeared to be fixed in this region. Peristalsis was definitely hyperactive, and the upper abdomen slightly tympanitic.

The temperature was 99°F., the pulse 90. The respirations were 22.

Examination of the urine was negative. The blood showed a red-cell count of 4,140,000 with 75 per cent hemoglobin, and a white-cell count of 14,000 with 78 per cent polymorphonuclears. The nonprotein nitrogen of the blood was 21 mg. per cent, and the serum chlorides were equivalent to 100 cc. N/10 sodium chloride. A blood Hinton test was negative.

A plain x-ray film of the abdomen showed a moderate quantity of gas in the small bowel and colon. The loops of small bowel were not appreciably dilated. There were no areas of calcification in the region of the kidneys, but small areas were seen in the true pelvis near the lower ends of the ureters.

A barium enema passed to the cecum without delay and entered the terminal ileum. An area of the colon at the junction of the descending portion and sigmoid showed a constant narrowing for a distance of about 5 cm. The mucosa throughout this area was intact, and no intraluminal defects were present. This area evidently corresponded to the palpable abdominal mass. On the films taken after evacuation barium was seen extending out into the soft tissues beyond the lumen of the bowel at the point of narrowing. Multiple small diverticula were seen throughout the sigmoid and lower descending colon. There was gas in the small bowel in close proximity to the lesion in the colon.

On the second hospital day a laparotomy was performed.

Differential Diagnosis

Dr. Edward L. Young: Cramplike abdominal pain in the abdomen associated with nausea is always indicative of some irritation of the bowel, and this may be anything from food injudiciously chosen to the partial obstruction of a malignant tumor. In this particular case it had persisted for a week, and that alone would seem to rule out a digestive upset. The abdominal borborygmi that are spoken of merely back up the diagnosis of irritation and suggest a partial obstruction. The "bearing down" sensation and the desire to defecate suggest that the trouble was fairly low down in the large intestine. The fact that he had had three to six watery movements a day for fifteen years suggests a habit peculiar to the individual rather than a background of disease. The lack of pus and blood also tends to rule out any ulcerative condition. The history suggests that there had been something present for at least three years. That, plus the facts that there had been no loss of weight or apparent change in his general condition and no evidence of abnormality in the stool, other than the looseness, would make cancer very unlikely.

On examination there was a slightly tender mass in the left iliac fossa, a slight fever and a somewhat elevated white count. The examination and laboratory work were otherwise essentially negative. The x-ray tells us that there was no evidence of growth in the large bowel even at the area corresponding to the palpable mass. It does add two facts of great importance, which, taken with the other evidence, would seem to make the diagnosis certain. First, there were diverticula in the sigmoid and descending colon and, secondly, the barium seemed to extend outside the lumen of the bowel into the soft tissue at the point where the mass was palpable. Although it is possible for a single diverticulum of the large bowel to exist and perforate, it is much more usual for them to be multiple, thus increasing the numerical chances of infection and perforation. In this individual it seems to me we are entitled to say with a very high degree of certainty that he has diverticulitis with perforation and abscess formation. I think the surgeon should plan his attack on that basis.

Is there anything else that should be considered seriously? We have ruled out cancer. Appendicitis and the other possibilities, such as solitary ulcer, amebic granuloma, and so forth, would seem to me too rare to be seriously considered.

Clinical Discussion

Dr. Richard H. Wallace: Dr. Arthur W. Allen operated on this case and found the mass to consist of a loop of sigmoid with an abscess on its mesial side walled off by small intestine. The abscess cavity contained about 120 cc. of thick foul pus, and when this was removed by suction, there was a necrotic defect in the sigmoid the size of a quarter. Closure of the defect seemed impossible and drainage on the mesial side, where small bowel could not be excluded, seemed unwise. The only reasonable alternative, even in the presence of so much infection, was resection; this was done by freeing the sigmoid and removing the involved area. The two ends of the cut sigmoid were brought out close together in the wound. Stab-wound drainage was established in the lateral gutter where the retroperitoneal space was opened to free the sigmoid. The patient had a surprisingly smooth convalescence and has since had the ends of his sigmoid united so that he is at present quite well.

Clinical Diagnosis

Diverticulitis of sigmoid.

Dr. Young's Diagnosis

Diverticulitis of sigmoid, with abscess formation.

Anatomical Diagnosis

Diverticulitis of sigmoid.

Pathological Discussion

Dr. Benjamin Castleman: The resected specimen of sigmoid contained several small diverticula, the largest measuring about 1.5 cm. in depth and 0.5 cm. in diameter. The mucosa around one of these diverticula was markedly congested and further exploration showed that this one opened into the ragged abscess cavity in the pericolic fat that was broken into at operation. The surrounding fat was quite indurated. Histologically there was no evidence of cancer.

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DIFFERENCES IN OPPORTUNITIES FOR HEALTH

Perhaps one of the greatest problems before humanity is the lack of application of accurate knowledge to the prevention and cure of illness.

Although we are confronted with certain unsolved questions relating to etiology and treatment of disease, science has brought to full understanding the essential facts of so large a proportion of the disorders of human beings that the sum total of medical and allied resources outweighs the deficiencies. But even so the preventable diseases are not being prevented and the curable ones are not being cured, to a deplorable degree.

If there is doubt about the truth of this last statement, the article under the above caption by Mountin and O'Hara in *Public Health Reports* (*53*: 485-496, 1938) may be read with interest. These authors record statistical evidence showing the relative incidence of illness existing in families comprising certain groups, living under different financial resources. For example, the rate in families on relief exceeded that among the gainfully employed by a large figure, thereby indicating that poverty is an important determining factor.

The study of this subject necessarily includes the relation of preventive medicine to the problems involved. In this latter field, agencies other than those connected with services rendered by physicians share with the practitioner the responsibility of dealing with existing conditions.

How far poverty is an indication of low intelligence or misfortune is an important question in dealing with human distress. Here the attitude of the state has its place, for the ratio of illness in families with incomes of $3,000 or more of 156 per 1000 persons, as compared with 188 in the less than $1,000 group and 262 for those on relief, calls for explanatory studies. Mortality as well as morbidity rates in these several income groups seem to carry the same implication as that shown by statistics relating to deaths due to tuberculosis, pneumonia, cancer, heart and kidney diseases, infantile diseases and accidents.

So far as inadequate medical care is a contributory factor in ill-health, there was evidence tending to show that the lower the income the less medical service is rendered, except in the group of hospitalized indigents. The statistics relating to surgery are also of interest in this respect, for people with little money are apt to neglect surgical attention except in emergencies.

In dealing with all health matters there seems to be a tendency, among certain people, to regard the medical profession as blameworthy for unsatisfactory conditions, and too often there have grown out of this misconception arguments for state medicine which, in the opinion of some politicians, seem to require the employment of physicians for the treatment of all illness at government expense.

A consideration of all factors involved in this subject shows that medicine alone is not the cure-all for existing conditions, but that together with

medicine there must be the co-ordinate confluence of public-health, social and economic measures. Even with all these agencies geared to high efficiency, progress will depend in large measure upon the higher average intelligence of the people. Ignorance, prejudice and shiftlessness are now, and will be for some time to come, obstacles in the way of better health.

Medicine will do its part individually and collectively. It only asks for fair and courteous treatment by the people.

A CENTURY OF MEDICINE

THE most important period of time through which the world has ever passed, or is likely to pass, is one's own lifetime. From the heights of our sophistication of animation we look back with real pity upon the dweller in the Dark Ages, groping in the shadows of the intellectually unenlightened period in which he lived. To him, however, there were no Dark Ages except, perhaps, in history. As with us and as with our grandfathers of the incriminating horse and buggy addiction, so with him; he lived in the glorious present, the future yet unborn, the past usually forgotten.

Our past one hundred years, however, have been different, according to Dr. Major G. Seelig, director of research of the Barnard Free Skin and Cancer Hospital, St. Louis, in an address before the St. Louis Medical Society on the occasion of its centennial celebration last April, which was recently published in *Science*. The seventeenth century, Dr. Seelig tells us, was a time of individualism run riot with great writers, great painters, great musicians and great philosophers, and in medicine, Harvey and van Leeuwenhoek.

The eighteenth century was one of "tedious and platitudinous formalizing" with only such high lights as Morgagni, the Hunters, Jenner, Auenbrugger and Benjamin Rush, but following it came the later renaissance of the nineteenth century. During this century what we know as modern man emerged, and in this century modern medicine began, established on the theories of evolution, the atomic theory of Dalton, the law of the conservation of energy, the establishment of organic chemistry and the annihilation by Pasteur of the doctrine of spontaneous generation.

With this roadbed prepared on which modern vehicles could move, we were ready for surgical anesthesia, and the nearly simultaneous discoveries of nitrous oxide, ether and chloroform. We were ready for antisepsis and asepsis, and modern surgery; we were waiting for cellular pathology, bacteriology, epidemiology and sanitation; experimental physiology was bound to come, and Roentgen and the Curies needed only their opportunity.

One lesson to be borne well in mind, however, is that no tub rests entirely on its own bottom. The accomplishments of any period are dependent on those of the period that preceded it. Dr. Seelig well recognizes this in closing his address with Tennyson's quatrain:

> Read my little fable;
> He that runs may read.
> Most can raise the flowers now,
> For all have got the seed.

MASSACHUSETTS MEDICAL SOCIETY

SECTION OF OBSTETRICS AND GYNECOLOGY

RAYMOND S. TITUS, M.D., *Secretary*
330 Dartmouth Street
Boston

CASE HISTORY NO. 75. PARTIAL PLACENTA PREVIA

A forty-eight-year-old Irish-American nonipara was admitted to the hospital at term for the treatment of vaginal hemorrhage. She had had crampy abdominal pains and backache for three weeks preceding entry. She had passed considerable bright-red blood by vagina one week before entry. There was some staining and the passage of clots daily during the next week until the night before entry, when she had another alarming hemorrhage. The bleeding was not associated with pain.

The family history was negative. The patient had always been well. She had had seven normal full-term deliveries and one miscarriage at the third month. Her menstrual periods began the age

A series of selected case histories by members of the section will be published weekly.

Comments and questions by subscribers are solicited and will be discussed by members of the section.

of thirteen and had always been regular and normal except for interruptions due to pregnancy.

Physical examination revealed a well-nourished, normally developed woman. The skin was dry and slightly pale. The general physical examination was negative except for varicosities of both lower legs and the vulva, and edema of both ankles. The temperature was 98.6°F., pulse 84, respirations 20 and blood pressure 128 systolic, 90 diastolic. There was some old and fresh blood about the vulva. Abdominal palpation revealed a term pregnancy, position LOA, uterus of normal consistence, and fetal heart absent. The pelvic measurements were: intercristal, 32 cm.; interspinous, 31 cm.; external conjugate, 20 cm.; and transverse diameter of the outlet, 9 cm. A catheter specimen of urine was straw-colored and acid, and contained a large trace of albumin. The sediment was negative, as was an examination for sugar.

The patient was immediately grouped for transfusion and prepared for examination. Under gas-oxygen and ether anesthesia, the cervix was found to be two-fingers dilated. There was a partial placenta previa, which accounted for the vaginal hemorrhage. A Braxton-Hicks' version was easily performed. One foot was pulled down into the vagina. A dead and macerated baby was delivered in twenty minutes by means of strong traction on the leg. There was moderate difficulty with the aftercoming head. The baby weighed 9 lb. The cervix was inspected because of profuse bleeding. A right lateral tear was repaired with interrupted chromic catgut sutures.

The patient was transfused with 500 cc. of citrated blood. The blood pressure was 64 systolic, 42 diastolic, fifty minutes after delivery; the pulse was 96, and the respirations 20. In spite of the transfusion the patient began to complain of air-hunger and went into severe shock within a half hour. A second transfusion was administered. Her condition, however, did not improve, so a supracervical hysterectomy was performed under light gas-oxygen and ether anesthesia. A rupture of the uterus into the right broad ligament was encountered at laparotomy. This rent was repaired following amputation of the uterus. One drain was inserted through the cervix and another was brought out through the abdominal wound. Since her condition was very poor at conclusion of the operation, she was given a third transfusion. The blood pressure then rose from 50 systolic to 80. During the next four days she received fluids by intravenous and subcutaneous injections, as well as two more transfusions. She developed, however, rapidly increasing abdominal distention which was not relieved by Pituitrin, enemas and flaxseed poultices. She expired on the fourth day, with signs of general peritonitis.

Comment. This is a very interesting case. The large trace of albumin and the dead baby suggest a toxemia with a separation of the placenta, but the examination revealed a partial placenta previa. It may well have been that the toxemia was the cause of the dead baby and the separation of the placenta. It is not at all common for placenta previas to bleed enough to cause intrauterine death unless the mother is exsanguinated.

The treatment of this case was poor. A bag probably would have been quite successful. As the partial previa was a very minor affair, rupture of the membranes alone might have been sufficient. The Braxton-Hicks' maneuver should have been carried through conservatively, a leg merely being brought through the cervix to act as a tamponade and the rest of the delivery left to nature. Rapid delivery caused this ruptured uterus, and the death is definitely attributable to the management of the case rather than to the partial previa, which was the cause of the bleeding.

DEATHS

HEALY — Harrison T. Healy, M.D., of New Bedford, died June 1. He was in his fifty-sixth year.

Born in New Bedford, he was graduated from high school, received his doctor of pharmacy degree from the Massachusetts College of Pharmacy and was awarded the degree of doctor of medicine from the Baltimore Medical College in 1907. Dr. Healy began practice in New Bedford and served as physician to the welfare department and as parochial school medical inspector.

A former fellow of the Massachusetts Medical Society, he was a member of the New Bedford Medical Society and the Massachusetts Clinical and Surgical Association.

His widow, four sons, two daughters, a brother and a sister survive him.

ILSLEY — Frederick R. Ilsley, M.D., of Medford, died April 28. He was in his sixty-ninth year.

Dr. Ilsley received his degree from the Harvard Medical School in 1892. He was a fellow of the American Medical Association and a retired fellow of the Massachusetts Medical Society.

MISCELLANY

DANGEROUS TICK BITES AVOIDABLE BY A FEW SIMPLE PRECAUTIONS

Fear of the tick that carries Rocky Mountain spotted fever in the East need not keep people indoors this summer. The tick's principal danger lies in its bite. Bites can be avoided by a few simple precautions, according to Dr. F. C. Bishopp, of the Bureau of Entomology and Plant Quarantine, United States Department of Agriculture. At the same time, Dr. Bishopp emphasizes, failure to take these precautions may have serious consequences. The East has an unusually large number of common dog, or wood, ticks this year — some being reported for the first time from vacant city lots. Even though only one in several hundred of these ticks may carry the fever virus, that one tick, which cannot be distinguished from the rest,

is an agent of death. No cure for Rocky Mountain spotted fever is known. Its mortality rate is one out of every five persons infected.

After passing the first part of its life as a small parasite on field mice, the tick waits in tall grass and underbrush for larger host animals. Cutting all grass and underbrush around houses and pathways, therefore, is one way to protect dogs and people from tick bites.

Keeping ticks from gorging themselves on the blood of dogs is another protective measure. A pair of forceps is all that is needed in removing ticks from dogs to which only a few have attached themselves. Dusting every five days with derris powder is necessary for dogs supporting a large number of ticks. Ticks should be handled with great care, Dr. Bishopp points out. Infection can be contracted by crushing a tick full of blood from an animal that has had the fever.

Boots laced up over trouser legs protect men walking through tick-infested areas, as ticks are usually picked up from grass or weeds close to the ground. Ticks always work their way upward before attaching themselves to their human host. The back of the neck and head are are their favorite feeding places. Careful examination of heads, especially children's, at least twice a day, will reveal the presence of a tick in time to prevent a fatal bite. Examination of the whole body is necessary after exposure to ticks. An effective way to de-tick clothes is to place them in a vessel that can be tightly covered, and set on top of them a pan containing half a teacupful of carbon tetrachloride or carbon disulfide. A few hours of such fumigation kills the ticks.

"Don't wait for the doctor to remove a tick," Dr. Bishopp warns. The important thing is to get the tick off as soon as possible. Anyone can disinfect the bite and the surrounding tissues by inserting into the exact spot where the tick was attached a round toothpick that has been dipped in iodine and drilling it in slightly.

The American dog tick is widely distributed throughout the United States east of the Rocky Mountains, as well as in western and northern California and in parts of Oregon. It is most numerous along the eastern coast from Massachusetts to Florida, especially within a few miles of the shore. Both Texas and Florida have a great many ticks — also some inland areas, such as southern Iowa and parts of Wisconsin and Minnesota. Islands off the coast of Massachusetts are heavily infested with ticks, especially Martha's Vineyard, Nantucket and Naushon. Tick numbers fall off along the sea coast from Marion, Massachusetts, westward. The Narragansett Bay islands are rather heavily infested. A few ticks have been reported on the west side of that bay and as far west as Stonington, Connecticut. There are large numbers of ticks on Long Island, especially the eastern half, and along Chesapeake Bay in Maryland. They are rarely seen west of the Blue Ridge. — *United States Department of Agriculture.*

WHAT MIDWESTERN SMALL-CITY FAMILIES SPEND FOR MEDICAL CARE

Midwestern small-city families are more likely to economize by not seeing the dentist, the oculist or even the doctor than by not buying supplies for the family medicine chest, when funds run low. This tendency is indicated in a table of medical expenditures for 3118 native white non-relief families living in seven representative cities in five midwestern states. The table is a part of a nationwide study of how much money the American family makes and how it is spent, conducted under the direction of Dr. Louise Stanley, chief of the Bureau of Home Economics, United States Department of Agriculture. The cities studied were Lincoln, Illinois; Boone, Iowa; Columbia and Moberly, Missouri; Mount Vernon and New Philadelphia, Ohio; and Beaver Dam, Wisconsin.

Low-income families consult dentists less frequently than doctors, and visits to the oculist usually are omitted entirely. But a majority of families at all income levels (67 to 92 per cent) reported expenditures for medicines and drugs during the twelve-month period studied in 1935-36. Amounts spent for medicine, however, were not high, averaging $6 to $21 per family per year at the different income levels. Averages were based on all families including those that made no purchases for the medicine chest.

Income for the year reached the $500 level before as many as half the families reported expenditures for a physician. Incomes of nearly three times this amount ($1250-$1499) were reached before as many as half the families had any expense for the dentist during the year. Even at the $4000-$4999 level only one family in four paid an oculist fee.

Fewer than 40 per cent of the families in the lowest income class studied ($250-$499) spent money for doctors' fees during the year; fewer than 12 per cent spent for dentists' services; and none of these families incurred any expense for an oculist. However, 67 per cent bought some medicine.

Approximately half the families in the second lowest income class studied ($500-$750) had expense for the physician; one in four, for the dentist; and practically none — less than 0.5 per cent — for the oculist. Three families out of every four bought some medicine-chest supplies.

Nearly all families of income levels above $500 (90 to 99 per cent) had some expenditure for medical care during the year. But even at the highest income level studied ($5000 to $10,000) only three families in four reported expense for a physician; four families in five for a dentist; and fewer than one in four for an oculist.

"It is evident that a majority of families with very low incomes did not have periodic physical examinations by a doctor and did not have the condition of their teeth checked regularly by a dentist," says Dr. Stanley. "Average amounts spent for medical care in low-income groups were not sufficient to pay for such routine services for all family members, even if the costs of serious illnesses had not been added in many instances. Since it is likely that families with low incomes need even more medical care than those that are well-to-do, these figures seem to indicate inadequate health measures. They support the contention of many social workers and others, that society should help provide adequate medical care for those who cannot pay the cost." — *United States Department of Agriculture.*

NOTES

The University of Montreal has conferred the doctorate of science on Dr. M. L. Fernald, Fisher professor of natural history at Harvard University. The presentation was made preceding a course in botany given at the university by Dr. Fernald. — *Science,* June 3, 1938.

* * *

Thirty-three appointments to the teaching and research staff of the Harvard Medical School were recently announced as follows:

Franz J. Ingelfinger, M.D., Harvard '36, as assistant in medicine; John C. Larkin, M.D., Johns Hopkins '35, as assistant in roentgenology; Joseph Meyer, M.D., Northwestern '36, as assistant in medicine; Lewis Dexter, M.D., Harvard '36, as research fellow in medicine; Arnold Iglauer, M.D., Cincinnati '37, as research fellow in medicine; Robert

M. Kark, D.C.H., London '37, as research fellow in medicine; Max J. Klainer, M.D., Boston University '37, as research fellow in medicine; Paul Kunkel, M.D., Washington University, St. Louis '34, as research fellow in medicine; Jesse C. Lockhart, M.D., University of Texas '35, as research fellow in medicine; Eugene L. Lozner, M.D., Cornell '37, as research fellow in medicine; John A. Luetscher Jr., M.D., Johns Hopkins '37, as research fellow in medicine; Jack D. Myers, M.D., Stanford '36, as research fellow in medicine; Reno R. Porter, M.D., Medical College of Virginia '35, as research fellow in medicine; Lowell A. Rantz, M.D., Stanford University '36, as research fellow in medicine; Andrew Yeomans, M.D., Harvard '35, as research fellow in medicine; William D. King, Jr., M.D., Baylor University '36, as research fellow in medicine; Alfred W. Harris, M.D., Washington University, St. Louis '35, as assistant in medicine; Raymond DeL. Adams, M.D., Duke University '36, as assistant in neurology; Robert A. Clark, M.D., Harvard '34, as assistant in psychiatry; Charles M. Krinsky, M.D., Tufts '33, as assistant in psychiatry; George F. Sutherland, M.Sc., McGill University '32, as research fellow in neuropathology; Samuel F. Martin, M.D., Harvard '34, as assistant in ophthalmology; Garrett L. Sullivan, M.D., Harvard '34, as assistant in ophthalmology; William A. Elliston, F.R.C.S., England '34, as assistant in orthopedic surgery; Carroll B. Larson, M.D., University of Iowa '33, as assistant in orthopedic surgery; Joseph M. Kmecza, S.M., Purdue University '37, as research fellow in comparative pathology and tropical medicine; David H. Clement, M.D., Harvard '35, as assistant in pediatrics; Edward C. Curnen, Jr., M.D., Harvard '35, as assistant in pediatrics; Robert H. Smith, M.D., Northwestern University '37, as teaching fellow in physiology; George Austen, Jr., M.D., Harvard '34, as assistant in genito-urinary surgery; Henry F. Howe, M.D., Harvard '30, as assistant in surgery; Samuel Lowis, M.D., Harvard '34, as assistant in surgery; Charles E. MacMahon, M.D., Harvard '36, as assistant in surgery.

CORRESPONDENCE

ARTICLES ACCEPTED BY THE AMERICAN MEDICAL ASSOCIATION COUNCIL ON PHARMACY AND CHEMISTRY

To the Editor:

In addition to the articles enumerated in our letter of April 30 the following have been accepted:

Abbott Laboratories
- Dextrose 10 per cent in Ringer's Solution
- Ringer's Solution
- Tablets Phenobarbital Sodium-Abbott, 1 gr.
- Mixed Grass Pollen Extract, Decimal Dilution Set (Abbott)

Drug Products Co., Inc.
- Pulvoids Sulfanilamide, 5 gr.

Chas. C. Haskell & Co., Inc.
- Sulfanilamide Tablets, 5 gr.

Hospital Liquids, Inc.
- Viosterol (A. R. P. I. Process) in Oil

Lederle Laboratories, Inc.
- Antipneumococcic Serum Types V and VII (Lederle) Refined and Concentrated
- Antipneumococcic Serum Types IV and VIII (Lederle) Refined and Concentrated

Eli Lilly & Co.
- Ampoules Ephedrine Sulfate-Lilly, 1 cc., 0.025 gm.

Mallinckrodt Chemical Works
- Aminoacetic acid

Mulford Colloidal Laboratories
- Rhus Tox. Antigen-Strickler, packages of two 1 cc. syringes
- Rhus Venenata Antigen-Strickler, packages of two 1 cc. syringes

Parke, Davis & Co.
- Theelin
  - Ampules Theelin Aqueous, 1 cc.
  - Ampules Theelin in Oil, 1 cc.
  - Vaginal Suppositories Theelin
- Theelol
  - Kapseals Theelol, 0.06 mg.
  - Kapseals Theelol, 0.12 mg.

Sharpe & Dohme
- Tablets Sulfanilamide, 5 gr.
- Gas-Gangrene Antitoxin (Combined) Concentrated
- Gas-Gangrene Antitoxin (Combined) Unconcentrated

PAUL NICHOLAS LEECH, *Secretary.*
535 North Dearborn Street,
Chicago, Illinois.

REPORTS OF MEETINGS

HARVARD MEDICAL SOCIETY

A meeting of the Harvard Medical Society was held at the Peter Bent Brigham Hospital on March 8, Dr. A. Baird Hastings presiding.

The medical case was presented by Dr. Carl Shepard. The patient, a nineteen-year-old white male, had noted occasional swelling of his face and feet at irregular intervals for seven months. He had experienced blurring of vision for four months, and there had been nocturia for three months. He had boiled his urine, and found that it solidified in the container. Examination on entry to the hospital revealed generalized edema, ascites, bilateral hydrothorax, pulmonary congestion and retinal edema with white retinal exudate. The blood pressure was 190 systolic, 145 diastolic. The urine contained a large trace of albumin, and a few red and white blood cells. The urinary excretion of albumin amounted to 40 gm. per day. The blood nonprotein nitrogen and blood urea nitrogen were not elevated. The total protein of the blood serum was 3.5 mm. per cent, with reversal of the albumin-globulin ratio. The red-blood-cell count was 2,700,000, and the hemoglobin 48 per cent (Sahli). The phenolsulfonphthalein excretion was reduced to 25 per cent in two hours. The patient was given a high-protein, salt-free diet, and fluids were restricted to 1000 cc. per day. There was a marked diuresis and loss of 30 lb. in weight. Dr. Henry Christian remarked that this was a typical case of glomerular nephritis.

The surgical case was a forty-three-year-old white male, who had suffered a bout of phlebitis of his left leg twenty-five years previously and had subsequently developed swelling of the leg which had reached very large dimensions and had been subjected to two plastic operations nine years later. Seven years before entry he suffered an attack of multiple abscesses in the leg, and six months previously, after trauma to the lower leg, he again experienced sepsis in the water-logged tissues. On entry to the hospital the patient was febrile and showed a red, swollen, edematous leg, which measured 90 cm. in diameter at the mid-calf. After treatment with moist heat and elevation, the edema subsided and 30 lb. of weight were lost due to drainage of fluid from the leg. Two plastic

operations were performed by Dr. John Homans, with removal of large masses of fibrous, edematous tissue. Following each operation there were severe septic complications which were treated with Prontylin with good results. A third plastic operation was not followed by infection. Following granulation, very large Thiersch grafts were applied.

Dr. Homans commented on the case, and stated that it was unusual to observe a case of elephantiasis nostra complicated by a suppurative sort of infection. In experimental elephantiasis it has been noted that, with the rise in the protein percentage of the tissue fluids, the animals are prone to attacks of fever due to non-suppurative streptococci. This patient experienced suppurative attacks. The treatment consisted of removing all the tissue down to the muscle, bone, tendons, and so forth, beneath the aponeurosis.

Dr. John P. Peters, professor of internal medicine at Yale University School of Medicine, delivered the paper of the evening, speaking on the subject "Exchanges between Cells and Interstitial Fluids." Dr. Peters presented a résumé of experiments performed in attempts to elucidate the processes by which water and various solutes, particularly inorganic constituents, find their way back and forth between cells and the interstitial fluids by which they are surrounded. These experiments were of two kinds: first, experiments in which the red blood cell was used as a model of general cellular reactions; secondly, investigations on the distributions of various solutes in the body.

Although the red blood cell is highly differentiated and unique in many respects it was particularly suited for these experiments because it could be isolated for analysis from its interstitial fluid, and because its metabolic processes could be brought to a standstill by chilling.

There is good reason to believe that the contents of the red blood cell have the same osmotic pressure as the blood serum and are in osmotic equilibrium with the latter. This means that in spite of differences in composition of the two mediums, cells and serum contain, per unit of water, the same concentrations of osmotically active chemical components. The differentiation of the two mediums depends on the highly selective permeability of the cellular membrane, which appears to be quite freely permeable to water, urea and certain other simple organic compounds, and to glucose under certain conditions. If water is added to blood it distributes itself between cells and serum in the same proportions as the water which was originally present in these mediums. The cells will therefore swell. Since urea can cross the membrane freely it will have no effect on the volumes of the cells, and solutions of urea will act exactly like equal amounts of water. If the cells were not quite impermeable to protein, hemoglobin would escape into the serum. Since the molecular concentration of protein in the red cells is more than three times as great as that in the plasma, it might be expected that the osmotic pressure of the cellular contents would be far greater than that of the serum. It is, of course, a similar difference in concentration of protein between plasma and interstitial fluids that, according to the Starling theory, balances the hydrostatic forces of the blood pressure, thus retaining fluids in the blood stream. In the equilibrium between cells and serum, however, the unequal distribution of protein is compensated by impermeability to other substances, especially the cations, sodium, potassium, calcium and magnesium. A 150 millimolar solution of sodium chloride has the same effective osmotic pressure as serum and as the contents of the red blood cells; that is, it contains per unit of water the same concentration of osmotically active units that are restrained from crossing the cell membrane.

A series of experiments have proved that under certain standard conditions the human red blood cells are quite impermeable to the bases sodium, potassium, calcium and magnesium, and that, when the concentrations of base in the serum are changed, the cells give up or take on water in such proportions that the osmotic pressures in the two mediums always remain identical. The size and water content of these cells would seem to be entirely at the mercy of the serum in which they are bathed. These conclusions were verified by in vitro and in vivo experiments.

In the in vitro experiments it was also proved by direct analysis that no base passed into or out of the cells. In the in vivo experiments, however, when the same technics were applied, unmistakable changes in the base of cells were detected. These findings were made in the very experiments in which changes of cell water and analyses of serum gave no evidence of transfer of base. Such results seemed paradoxical.

Although there is slightly more total base in serum, the concentrations in cells and serum are sufficiently alike to give the impression that, in the cells as in the serum, inorganic salts are chiefly responsible for the effective osmotic pressure. If this is the case, since the osmotic pressure of both media is the same, the concentrations of base in cells and serum should vary directly. Such is not the case. While serum base varies within relatively narrow limits, cell base varies over a much larger range. Furthermore, there is no demonstrable correlation between the two. Therefore base cannot have as important an osmotic role in cells as it does in serum. Osmotic equilibrium can exist when the concentration of base is distinctly higher in the cells than in the serum. In this case a fraction of the base in the cells must be osmotically inactive (perhaps because it exists in non-ionized form). It appears that any variation of base in serum is attended by a proportional change of osmotic pressure, whereas the base of cells can vary within wide limits without affecting osmotic pressure. The contents of cells are complex and include substances which do not exist in serum, but which must exert osmotic pressure. Moreover, in the cell, metabolic processes cause continuous permutations and combinations of solutes. Were these processes not osmotically buffered by some mechanism, they would produce constant changes in the volume and water content of the cells. There must be some means by which cells can, in times of need, accumulate or eliminate stores of material without being forced to take on or to excrete, at the same time, excessive amounts of water,

Red cells cannot be as completely impervious to base as would be inferred from in vitro experiments, else they would be excluded from elements essential for their activities. The impermeability of the cell membrane may be only a facultative property. Although cells are found to be impervious to phosphate and other ions in the resting state, if they are studied at higher temperatures such as are encountered in the body and in which metabolic processes are allowed to proceed, phosphate and potassium pour out of the cell during the process of glycolysis. This process was found to be reversible and was not purely mechanical in nature, but definitely a part of the metabolic process.

The red blood cell, then, appears to be always in osmotic equilibrium with its environmental fluid, blood serum. It responds to changes of the concentration of base in serum by transferring water and thus changing its volume. Moreover, so long as it is in the resting state, its

membrane is impermeable to base, to phosphate and to sulfate. But during metabolic activity, base and phosphate pass in one direction or another, apparently in accordance with the needs of the cell. Movements of these substances are not accomplished merely by diffusion: they must involve chemical reactions.

Various experiments have indicated that the principles which control the exchanges of water and solutes between the red blood cells and serum also control the exchanges between the cells of all tissues and the interstitial fluid. Analyses have indicated that approximately 20 per cent of muscle tissue has the composition of an ultrafiltrate of serum; that is, so far as inorganic elements are concerned it contains chiefly sodium and chloride. Diffusion experiments indicate that there is a barrier in muscle tissue which differentiates about one fifth of the tissue from the other four fifths. Sodium, chloride and inorganic phosphate diffuse readily into one fifth of the muscle mass, but do not cross the barrier into the cell (under resting, stable conditions), while urea diffuses readily throughout the whole mass. Under the stimulus of glucose and insulin the concentration of phosphate esters in the muscle increased, indicating that, as in the red blood cell, the stimulus of metabolic activities initiated chemical processes which conveyed phosphate across the cell membrane that it ordinarily did not traverse.

The percentage of interstitial fluids was measured more directly by means of injecting substances which were not normal constituents of serum and which would pass freely through vascular walls without penetrating cells. Three substances were utilized for this purpose: a sulfocyanate, a sulfate and sucrose. Determinations of the distribution of these substances throughout the body again indicated that there is a barrier which separates the fluids of the body, in a broad way, into two compartments, of which one, into which these substances chiefly or solely diffuse, makes up roughly 20 to 30 per cent of the body weight.

By using the same principle but employing thio-urea, which possesses most of the chemical and physiological properties of urea but is excreted completely unchanged in the urine, an attempt was made to measure the total water in the body. The volume of distribution of this substance varied from 68 to 70 per cent of the body weight — values consistent with accepted conceptions of the water content of the body.

Studies of the distribution of sodium sulfate throughout the body after injection of hypertonic solutions of this substance again gave results compatible with the theory that sulfate, sodium, chloride, and sulfocyanate were distributed over an identical fraction of the total water of the body, and that this fraction, approximately one fifth of the body mass, increased in volume by one liter. This expansion in volume must have been accounted for by acquisition of fluid from other parts of the body, namely the cells, since the hypertonic solution increased the osmotic pressure of the interstitial fluid, and water was withdrawn from the cells to restore osmotic equilibrium.

Tissue cells, then, appear to resemble red blood cells in their general behavior; they seem to contain less sodium and to be more nearly if not completely devoid of chloride. When the concentration of sodium in the interstitial fluid changes, osmotic equilibrium is restored by transfers of water to or from the cells without transfers of base. There is no evidence that base is admitted to or discharged from the cells in behalf of osmotic equilibrium per se. The concentration of sodium in the interstitial fluids controls the water content or size of the cells. Consequently, it must determine the dilution of the cellular constituents. The actual quantities of these constituents in the cells, however, appear to be controlled by entirely different mechanisms. There must be some means by which potassium, phosphate and other chemical substances are restrained in the cell to protect the integrity of the cellular composition. It is equally essential that there be some means of dissolving this restraint when need arises in the cells for more of these materials or for the discharge of any excess. Apparently the regulation of these restraining forces is delegated to the metabolic processes of the cells, thus insuring automaticity.

The tissue cells differ from the resting red blood cells with respect to the passage of potassium across the cell membrane. Apparently potassium diffuses freely throughout all the water of the body, and in addition, variable amounts enter some or all the tissue cells. Whether or not this fraction is taken *into* the cells by means of diffusion, it must be restrained *within* the cells by some other mechanism. Phosphate diffuses freely through the interstitial fluids but not into the cells. A certain amount does penetrate the cells. It must be supposed that this fraction gains access to the cells and is there retained by something other than diffusion.

These phenomena may be correlated as follows: the cells and interstitial fluid are in osmostic equilibrium; this osmotic equilibrium is maintained in spite of the extreme diversity of the two mediums by virtue of the fact that the interposed membranes do not allow free interchange by diffusion of a variety of substances, especially protein, sodium, chloride and phosphate. Sodium and chloride, in fact, seem to be almost completely, if not completely, excluded from the cells, athough they are the chief inorganic components of interstitial fluid. It follows that any changes in the concentration of sodium in the interstitial fluid must result in an exchange of water that will restore equality of osmotic pressure between the two mediums. The volume of the intracellular fluid must therefore depend upon the concentration of sodium in serum. Ordinarily, the concentration of potassium in interstitial fluid is only a small fraction of the concentration found in cells. Nevertheless, when potassium salts are added to the system, potassium enters the cells in such proportions as to give the impression that extracellular and intracellular potassium are in simple diffusion equilibrium. If the cell membrane is freely permeable to potassium, this permeability must be restricted to a small fraction of the intracellular potassium, since the concentration of potassium in interstitial fluid is so low. The major portion of the intrinsic potassium of cells, since it does not diffuse outward, must be restrained from free diffusion by some force other than mere impermeability of the envelope of the cell.

Dr. Peters cited several observations illustrating the inferences to be drawn from the above stated hypotheses. Gamble found that in the dehydration of starvation acidosis potassium as well as sodium was wasted, a wastage which also occurred in the diuresis produced by acidifying salts. This wastage of potassium was not due to losses in extracellular sodium with resultant changes in intracellular potassium, since even with extreme depletion of body sodium there were only insignificant losses of potassium. In Addison's disease and in some animals after adrenalectomy, sodium wastage is accompanied by retention of potassium, although there is no rise of serum potassium. The potassium apparently enters or becomes imprisoned in the cells. Analyses of the tissues of rats after adrenalectomy have shown that there is an increase in cellular potassium without a comparable increase in water. This exemplifies the accumulation in the cells of osmotically in-

active potassium and suggests that removal of the adrenals gives rise to a widespread derangement of cellular metabolism. Adrenalectomized dogs are benefited by restriction of potassium in the diet and can be thrown into shock by administration of potassium salts. This is consistent with the hypothesis that the intrinsic potassium of the cells is affected by the supply of inorganic potassium in the interstitial fluid. Observations upon a case of Addison's disease indicated that potassium became more concentrated in the cells and showed that water and electrolytes moved in the directions indicated by the previously cited experiments.

Depletion of serum sodium is extremely common in clinical medicine. It is regularly encountered in the states of dehydration that result from severe vomiting, diarrhea or gastrointestinal fistulae, in diabetic acidosis, in water intoxication, in lobar pneumonia, in the terminal stages of nephritis and sometimes with no discoverable cause. It has been too generally assumed that in all these conditions, as well as in Addison's disease, depletion of base has the same quantitative and qualitative effects. Such is not the case, as is proved by the wide range of symptomatology associated with deficits of base and by the variability of the responses to restoration of the concentration of salt in the serum. Both the concentration of base in the interstitial fluids and the volumes of these fluids must be accurately measured if precise information is to be gained about the organism as an entity. In addition, the allocation of these fluids and solutes between the various compartments of the body cannot be neglected, since the animal organism is not homogeneous; and finally, the state and activity of these solutes are matters of no little importance.

NEW ENGLAND SOCIETY OF PHYSICAL MEDICINE

At the annual meeting of the New England Society of Physical Medicine, held at the Hotel Kenmore, Boston, on May 18, the following officers were elected: president, Dr. Hosea W. McAdoo, of Arlington; first vice-president, Dr. George B. Carr, of Lynn; second vice-president, Dr. Henry A. Tadgell, of Wrentham; secretary, Dr. William D. McFee, of Boston; treasurer, Dr. Howard Moore, of Boston; councilors for three years, Dr. David T. Percy, of Arlington, and Dr. Charles W. Bruninghaus, of Worcester.

Dr. Kristian G. Hansson, director of physical therapy, Cornell Medical Center, New York City, spoke on "Aftercare of Poliomyelitis." The paper was discussed by Dr. William T. Green.

NOTICES

SOUTH END MEDICAL CLUB

The next regular meeting of the South End Medical Club will be held at the headquarters of the Boston Tuberculosis Association, 554 Columbus Avenue, Boston, on Tuesday, June 21, at 12 o'clock noon.

Dr. Edward J. O'Brien will speak on "Twenty-five Years' Experience with Obstructing Prostates"; the talk will be illustrated with moving pictures of a transurethral resection of the prostate gland.

LAWRENCE CANCER CLINIC

The regular Lawrence Cancer Clinic, to be held at the Lawrence General Hospital, 1 Garden Street, Lawrence, on Tuesday, June 21, at 10:00 a. m., will be a demonstration and teaching clinic for physicians, with Dr. Channing C. Simmons present as consultant. Physicians of the north half of Essex County are invited to accompany any of their patients whom they desire to have this service or to send them with a note. A report will be returned to every physician who sends a patient. The service is gratis. Any physician is welcome to attend the clinic.

This clinic is endorsed by the Committee on Postgraduate Instruction of the Massachusetts Medical Society.

Roy V. Baketel, M.D.,
Charles J. Burgess, M.D.,
John J. McArdle, M.D.,
Harry H. Nevers, M.D.,
Thomas V. Uniac, M.D.,
J. Forrest Burnham, M.D., *Chairman.*

NEW ENGLAND HEART ASSOCIATION

There will be a special meeting of the New England Heart Association in the Ether Dome at the Massachusetts General Hospital, Wednesday, June 22, at 8:15 p. m.

Dr. George W. Pickering, from the Department of Clinical Research, University College Hospital, London, England, will speak on "The Problem of High Blood Pressure in Man."

Interested physicians and medical students are cordially invited to attend.

Edward F. Bland, M.D., *Secretary.*

SOCIETY MEETINGS AND CONFERENCES

Calendar of Boston District for the Week Beginning Monday, June 13

Tuesday, June 14
*10 a. m. - 12:30 p. m. Tumor clinic. Boston Dispensary.

Friday, June 17
*10 a. m. - 12:30 p. m. Tumor clinic. Boston Dispensary.

Saturday, June 18
*10 a. m. - 12 m. Staff rounds at the Peter Bent Brigham Hospital. Conducted by Dr. Henry A. Christian.

*Open to the medical profession.

June 10 and 11 — American Heart Association. Page 707, issue of April 21.

June 13, 14 and 15 — American Board of Obstetrics and Gynecology. Page 903, issue of May 26.

June 13-17 — American Medical Association. San Francisco.

June 13, October 8 and November 15 — American Board of Ophthalmology. Page 282, issue of February 10.

June 20-24 — Canadian Medical Association. Page 902, issue of May 26.

June 21 — South End Medical Club. Notice above.

June 21 — Lawrence Cancer Clinic. Notice above.

June 22 — New England Heart Association. Notice above.

June 23 — Pentucket Association of Physicians. Hotel Bartlett, 95 Main Street, Haverhill, 8:30 p. m.

September 12-14 — American Association for the Study of Goiter. Page 545, issue of March 24.

September 12-15 — American Congress of Physical Therapy. Page 946, issue of June 2.

October 17-21 — Clinical Congress of the American College of Surgeons, New York City.

October 24-26 — Academy of Physical Medicine, Scientific Session. Washington, D. C.

District Medical Societies

HAMPDEN
Meeting will be held on the fourth Tuesday in July.

PLYMOUTH
Meeting will be held at 11 a. m. on July 21.

BOOKS RECEIVED FOR REVIEW

Physiological and Clinical Chemistry. William A. Pearson and Joseph S. Hepburn. Second edition. 467 pp. Philadelphia: Lea & Febiger, 1938. $5.50.

Alfred Owre: Dentistry's militant educator. Netta W. Wilson. 331 pp. Minneapolis: The University of Minnesota Press, 1937. $4.00.

Child Care and Training. Marion L. Faegre and John E. Anderson. Fourth edition, revised. 327 pp. Minneapolis: The University of Minnesota Press, 1937. $2.50.

Pediatric Surgery. Edward C. Brenner. 843 pp. Philadelphia: Lea & Febiger, 1938. $10.00.

Surgical Anatomy of the Head and Neck. John Finch Barnhill. 921 pp. Baltimore: William Wood & Company, 1937. $20.00.

Organization, Strategy and Tactics of the Army Medical Services in War. T. B. Nicholls. 372 pp. Baltimore: William Wood & Company, 1937. $4.00.

Medico-Legal Aspects of the Ruxton Case. John Glaister and James Couper Brash. 284 pp. Baltimore: William Wood & Company, 1937. $6.00.

The Single Woman and Her Emotional Problems. Laura Hutton. Second edition. 173 pp. Baltimore: William Wood & Company, 1937. $1.50.

The Radiology of Pulmonary Tuberculosis. J. E. Banŋen. 156 pp. Baltimore: William Wood & Company, 1937. $4.50.

Diseases of the Thyroid, Parathyroids and Thymus. André Crotti. Third edition, thoroughly revised and enlarged. 1229 pp. Philadelphia: Lea & Febiger, 1938. $20.00.

Eat and Keep Fit. Jacob Buckstein. 128 pp. New York: Emerson Books, Inc., 1938. $1.00.

On a New Gland in Man and Several Mammals (Glandulae Parathyreoideae). Ivar Sandström. 44 pp. Baltimore: The Johns Hopkins Press, 1938. $1.00.

Pneumonia and Serum Therapy. Frederick T. Lord and Roderick Heffron. 148 pp. New York: The Commonwealth Fund, 1938. $1.00.

On Thought in Medicine. Hermann von Helmholtz. 27 pp. Baltimore: The Johns Hopkins Press, 1938. 75c.

A Biological Approach to the Problem of Abnormal Behavior. Milton Harrington. 459 pp. Lancaster: The Science Press, 1938.

Twenty-eight Years of Sterilization in California. 47 pp. Pasadena: The Human Betterment Foundation, 1938. 25c.

Demonstrations of Physical Signs in Clinical Surgery. Hamilton Bailey. Sixth edition, revised. 284 pp. Baltimore: William Wood & Company, 1937. $6.50.

Practical Methods in Biochemistry. Frederick C. Koch. Second edition. 302 pp. Baltimore: William Wood & Company, 1937. $2.25.

Hemorrhoids. Marion C. Pruitt. 170 pp. St. Louis: The C. V. Mosby Company, 1938. $4.00.

Symptoms of Visceral Disease: A study of the vegetative nervous system in its relationship to clinical medicine. Francis Marion Pottenger. Fifth edition. 442 pp. St. Louis: The C. V. Mosby Company. $5.00.

The Heart in Pregnancy. Julius Jensen. 371 pp. St. Louis: The C. V. Mosby Company, 1938. $5.50.

Bile: Its toxicity and relation to disease. O. H. Horrall. 434 pp. Chicago: The University of Chicago Press, 1938. $4.00.

Major Endocrine Disorders. S. Levy Simpson. 184 pp. London: John Bale Medical Publications, Ltd., 1938. 10/6d.

Practical Clinical Gynecology. Henry C. Falk. 393 pp. New York: American Journal of Surgery, Inc., 1938. $5.00.

Internships and Residencies in New York City, 1934-1937. Their Place in Medical Education. Report by the New York Committee on the Study of Hospital Internships and Residencies. 492 pp. New York: The Commonwealth Fund, 1938. $2.50.

Essentials of Obstetrical and Gynecological Pathology: With clinical correlation. Marion Douglass and Robert L. Faulkner. 187 pp. St. Louis: The C. V. Mosby Company, 1938. $4.75.

BOOK REVIEWS

The Biology of Pneumococcus: The bacteriological, biochemical and immunological characters and activities of diplococcus pneumoniae. Benjamin White. 799 pp. New York: The Commonwealth Fund, 1938. $4.50.

Occasionally a book appears which almost at once comes to be known as a standard work of reference. This extensive monograph on the pneumococcus by Dr. White and his collaborators will surely take its place among this class. With thoroughness and scholarly accuracy which could not be surpassed by the most laborious of the German scientific writers of the past, the senior author has read and re-read the significant literature on the subject, both old and new, and then in the light of his long experience has fashioned these multitudinous fragments into a lucid and critical account of the various aspects of what he most accurately characterizes as this amazing cell.

In the beginning there is an interesting statement of the early history of studies concerning the pneumococcus. In reading it, once again we are filled with respect and admiration for the pioneers who brought order and light to the chaos and darkness that confronted them. During the last quarter of the nineteenth century the etiological role of the pneucococcus in most cases of lobar pneumonia was definitely established — not by any means a simple demonstration when we consider the variegated flora encountered in sputa and the difficulty, now hardly overcome, of producing experimentally the disease in anything like its natural manifestations. By this time, too, many of the fundamental facts concerning the cultivation, identification and antigenic attributes of the pneumococci were recorded. It is chastening to consider that much of the work of the past thirty-eight years has consisted in widening and leveling the paths which Pasteur, Fränkel, Denys, Mennes, Metchnikoff and others had so unerringly demarcated. In the following chapters, each of which may be regarded as a compendious though nonetheless comprehensive monograph on its specific subject, the authors treat of the biologic characteristics of the pneumococci, their classification, dissociative phases, degrees of pathogenicity for man and animals, and their chemical composition, especially in respect to antigenic structure. The final pages deal with the complex factors involved in the resistance of the animal body to infection with [illegible] micro-organisms. Here we are given along with what is known concerning the mechanisms of pneumococcal immunity, practical information concerning the technics of active immunization by means of vaccines, as well as the most recent methods of producing efficient antiserums to be used in the treatment of lobar pneumonia. After a brief account of the rationale of specific therapy and an assay of the results which have been obtained in the clinic through

its use, the text concludes with a statement of unsolved problems.

The appendix includes descriptions of the laboratory procedures employed in the bacteriological and serological study of the pneumococcus and in the preparation of antiserums, and finally an admirably arranged bibliography of nearly sixteen hundred items which cannot fail to become indispensable to both student and investigator alike.

In wholeheartedly recommending this book to all who have any concern with these organisms and their effects, the reviewer cannot refrain from expressing his regret that Dr. White could not have lived to see his excellent treatise accorded those honors which it so manifestly deserves.

Lebens-Versicherungs-Medizin. Felix Deutsch and Fritz Stern. 282 pp. Vienna: Emil M. Engel, 1938.

Life-insurance medicine, as a systematic and comprehensive study of the ratings of extra-mortality (substandard risks), has very seldom been treated in a form which could justifiably be called a *book of reference*. In the book which has just been published, the authors have fulfilled precisely this *practical* requirement.

Medical directors and examining physicians of life-insurance companies will find in this book an indispensable aid for their daily work. Medical advisers will gain from it the necessary comprehension of the theoretical basis and the practical requirements of their practice as life-insurance physicians, which is often not their main professional activity.

In addition to this, the book gives a systematic insight into a medical field whose importance for medicine — considering the high place of life insurance in the entire economic sphere — is not always fully realized by physicians. In order to show the doctor who is not familiar with life-insurance medicine its connections with general medicine, the authors have covered the clinical as well as the statistical point of view.

The introduction contains the following remarks:

> It is obvious that the ratings found in this book will not be primarily new ones; it was frequently necessary to use standard ratings which are already known. Nevertheless we have given new ratings for a considerable number of symptoms and diseases and have also attempted to establish ratings for impairments which have seldom or never before been rated. Finally, we have sought to describe and classify the impairments for which we have given ratings on the basis of recognized clinical findings. We have, moreover, supplemented the section on insurance medicine by a description of the applicable methods of examination and by a list of occupational and athletic hazards, as well as by an attempt to give ratings for the additional risks (supplementary insurance for invalidism and accidental death).
>
> We believe that the essential quality of this book consists in the following features: (1) that all fields of medicine, insofar as they have any relation to insurance medicine, have been covered; (2) that the systematic classification and revision of the material have permitted us to discuss all combinations and bases of clinical symptoms which are important for insurance medicine; (3) that we have ventured to give definite standard ratings, in order to create a uniform objective basis for the premium, excluding all subjective interpretations, as a starting point for further investigations in this field; and (4) that, in order to advance insurance medicine as a science, we have considered it necessary to dispense with the reticence which has formerly been maintained in the publication of standard ratings, and we have thus made the rating of substandard risks a subject for detailed discussion.

Lectures on the Epidemiology and Control of Syphilis, Tuberculosis, and Whooping Cough, and Other Aspects of Infectious Disease. Thorvald Madsen. The Abraham Flexner Lectures Series No. 5. 216 pp. Baltimore: The Williams & Wilkins Company, 1937. $3.00.

This is a book of two hundred pages, containing the fifth series of the Abraham Flexner Lectures, given by Dr. Madsen at Vanderbilt University in March, 1937. It is the sort of material the reviewer at first thought he would skim through lightly, but he found himself held to reading Dr. Madsen's lectures page by page and line by line.

Five subjects are dealt with as follows: "Control of Venereal Disease in Denmark, with Special Reference to Syphilis"; "Mechanism of Bacterial Infection"; "Tuberculosis in Denmark"; "The Influence of Seasons on Infection"; "Whooping Cough."

The reader is impressed with the advanced social organization and unity of Denmark. This comes to the surface in many ways. Tuberculous cattle were killed and paid for by the government before the turn of the century; the first tuberculosis seals were sold there in 1904; and we are reminded of the contributions of Finsen and other famous Danes.

Dr. Madsen is more than a public-health worker; to the reviewer it seemed as though physiology was his basic interest, yet nowhere within this volume does he deal with essential physiological subjects.

The book is an entertaining little volume and the material contained within must have formed an interesting group of lectures.

How Ancient Healing Governs Modern Therapeutics: The contribution of Hellenic science to modern medicine and scientific progress. Kleanthes A. Ligeros. 523 pp. New York and London: G. P. Putnam's Sons, 1937. $10.00.

One would look far to find a drearier book than this. The author takes a deal of space to prove what requires no proving; namely, that much that is most worth while in modern thought and civilization had its roots in ancient Hellas. To assume as he does, however, that practically every important measure used in treating the sick was possessed by the Greeks is a manifest absurdity. As to Hellenic concepts actually governing modern therapeutics, his real complaint is that a good many procedures which the Greeks thought valuable have been discarded by the medical profession, in particular chiropraxis or manipulation of the spine.

But a fallacious thesis is not all that is the matter. There is a dearth of information from original sources, and even what is furnished is not entirely apropos. Nor, unfortunately, has Dr. Ligeros any gifts as a writer. He is wordy, repetitious and prosy, and still worse, is given to unsubstantiated statements, and careless about the names of those he quotes and in his proofreading. Thus empyema is repeatedly "empyemia." And since when did the fallopian tube lead from the pharynx to the ear?